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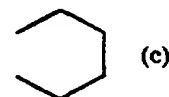
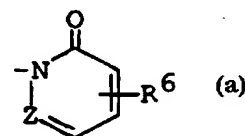
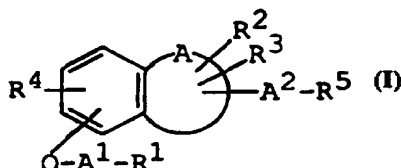
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(54) Title: NAPHTHALENE DERIVATIVES AS PROSTAGLANDIN I2 AGONISTS

(57) Abstract

A compound of formula (I) wherein, R¹ is carboxy or protected carboxy; R² is hydrogen, hydroxy or protected hydroxy; R³ is hydrogen, hydroxy, protected hydroxy, etc.; R⁴ is hydrogen or halogen; A¹ is lower alkylene; A² is bond or lower alkylene; -R⁵ is (a) (in which R⁶ is mono(or di or tri)aryl(lower)alkyl and Z is N or CH), etc.; and (b) is (c), etc.; and a pharmaceutically acceptable salt thereof which are useful as medicaments.



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DESCRIPTION

NAPHTHALENE DERIVATIVES AS PROSTAGLANDIN 12 AGONISTS

5 TECHNICAL FIELD

This invention relates to new naphthalene derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

10 BACKGROUND ART

Some naphthalene derivatives have been known as described, for example, in EP 0542203A2.

DISCLOSURE OF INVENTION

15 This invention relates to new naphthalene derivatives. More particularly, this invention relates to new naphthalene derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities such as an inhibitory activity on platelet
20 aggregation, vasodilating activity, antihypertensive activity or the like and are prostaglandin I₂ agonists, to processes for their production, to a pharmaceutical composition containing the same and to a use thereof for manufacture of medicaments.

25 Accordingly, one object of this invention is to provide new and useful naphthalene derivatives and pharmaceutically acceptable salts thereof.

Another object of this invention is to provide processes for production of the naphthalene derivatives
30 and salts thereof.

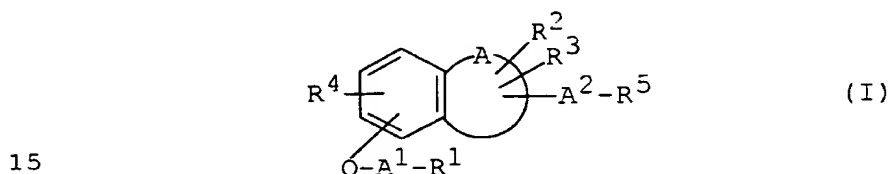
A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, said naphthalene derivatives or pharmaceutically acceptable salts thereof.

35 Still further object of this invention is to provide

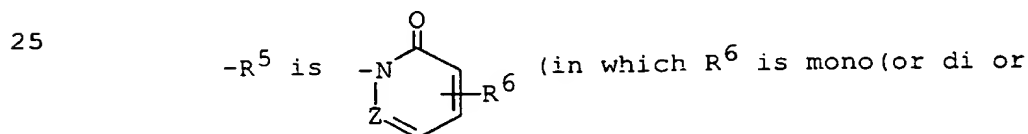
- 2 -

use of the naphthalene derivatives and pharmaceutically acceptable salts thereof for manufacture of medicaments for the therapeutic and/or prophylactic treatment of arterial obstruction, cerebrovascular disease, hepatic
 5 cirrhosis, arteriosclerosis, ischemic heart disease, restenosis after percutaneous transluminal coronary angioplasty, hypertension or the like.

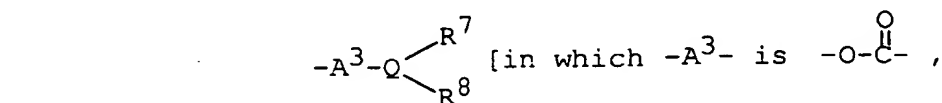
The naphthalene derivatives of this invention can be
 10 represented by the following formula (I) :



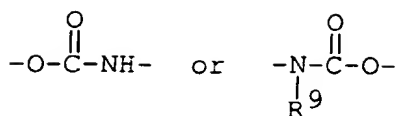
wherein R^1 is carboxy or protected carboxy,
 R^2 is hydrogen, hydroxy or protected hydroxy,
 R^3 is hydrogen, hydroxy, protected hydroxy,
 20 lower alkyl or halogen,
 R^4 is hydrogen or halogen,
 A^1 is lower alkylene,
 A^2 is bond or lower alkylene,



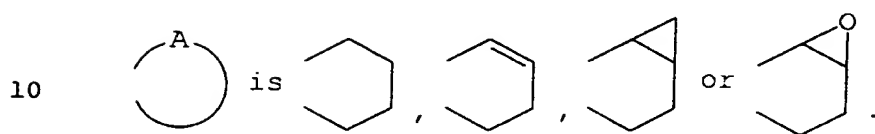
30 tri)aryl(lower)alkyl and Z is N or CH), or



- 3 -

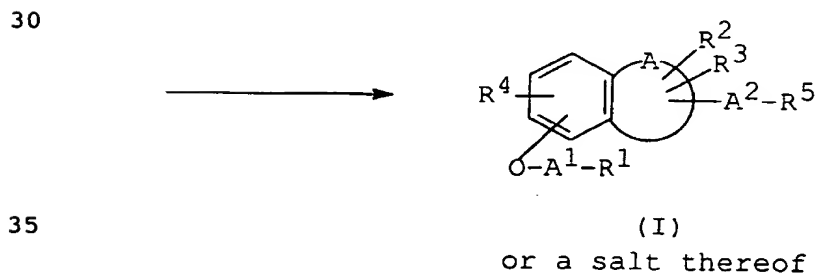
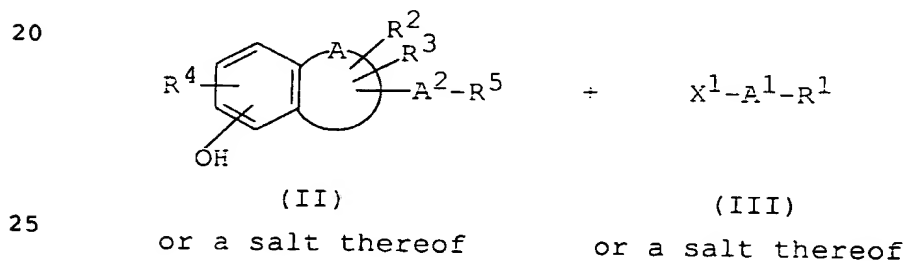


5 (wherein R^9 is hydrogen or lower alkyl),
 10 Q is N or CH, R^7 is aryl and R^8 is aryl], and

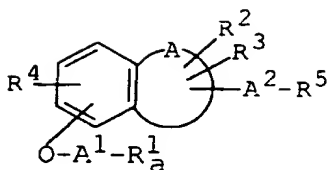


15 According to the present invention, the new
 naphthalene derivatives (I) can be prepared by the
 processes which are illustrated in the following scheme.

Process 1



- 4 -

Process 2

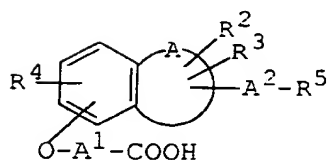
(Ia)
or a salt thereof

10



Elimination reaction of
the carboxy protective group

15

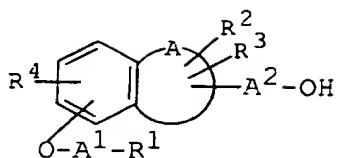


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(Ib)
or a salt thereof

Process 3

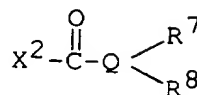
25



30

(IV)
or a salt thereof

+



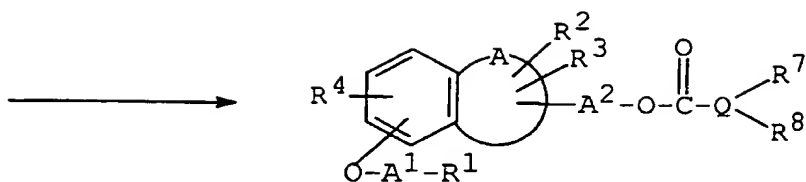
(V)

or a salt thereof

35

- 5 -

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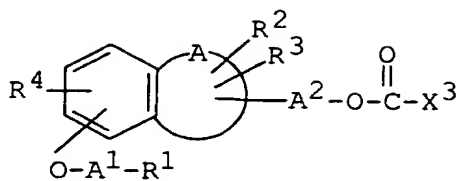
(Ic)

or a salt thereof

10

Process 4

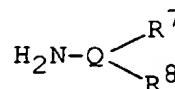
15



(VI)

or a salt thereof

+

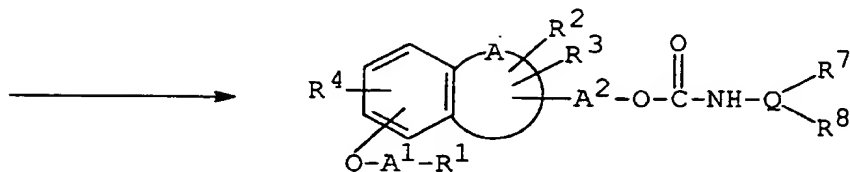


(VII)

or a salt thereof

20

25



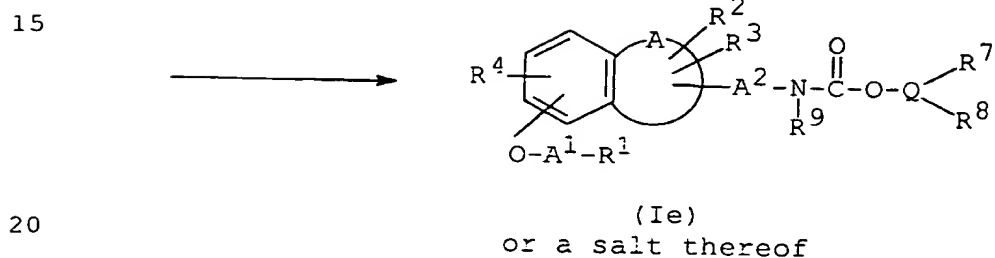
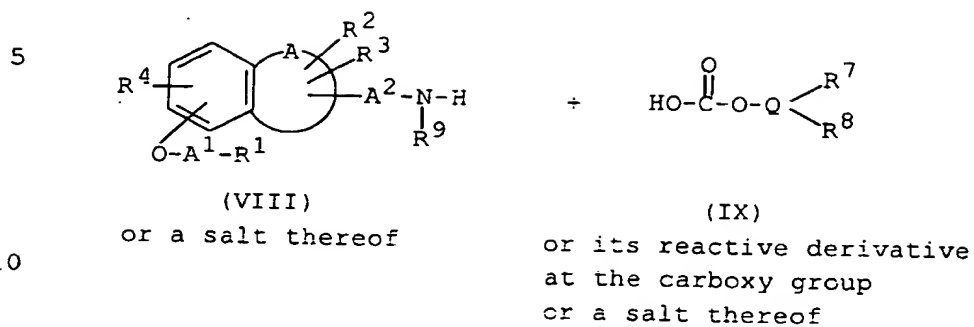
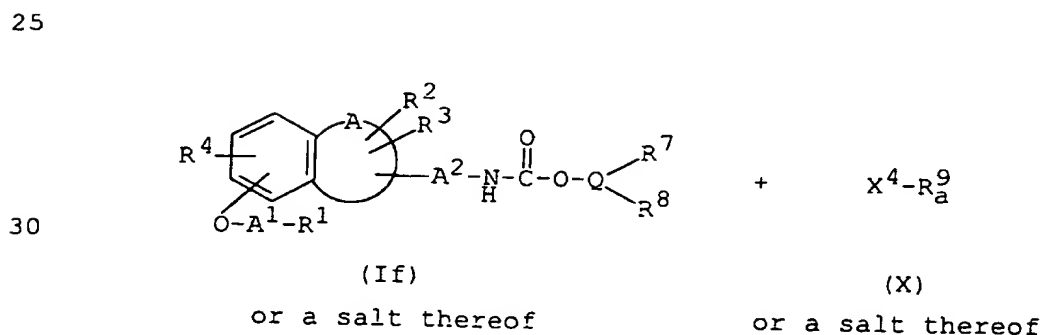
(Id)

or a salt thereof

30

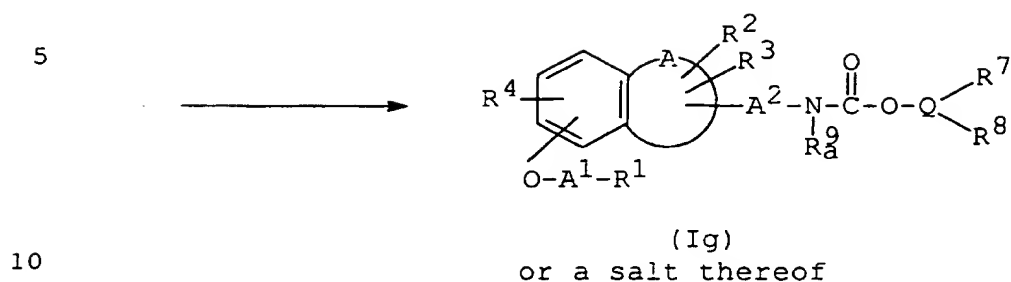
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- 6 -


Process 5Process 6

35

- 7 -



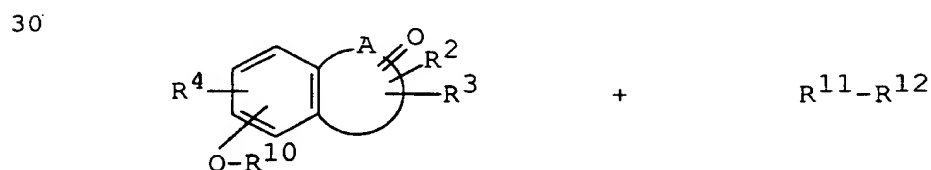
wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , R^9 , A^1 , A^2 , Q and

15  are each as defined above,

20 X^1 is acid residue,
 R_a^1 is protected carboxy,
 X^2 is halogen,
 X^3 is halogen,
 X^4 is halogen, and
 R_a^9 is lower alkyl.

25 Some of the starting compounds are novel and can be prepared by the following processes.

Process A

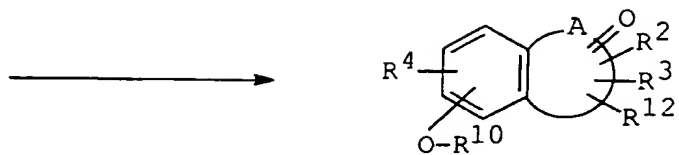


or a salt thereof

(XII)
or a salt thereof

- 8 -

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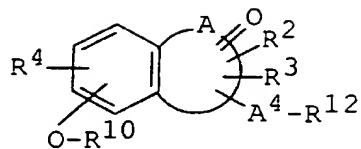


(XIII)
or a salt thereof

10

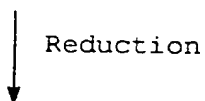
Process B

15

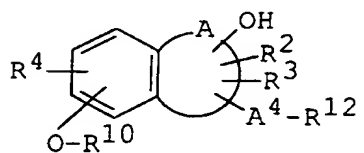


(XIV)
or a salt thereof

20



25

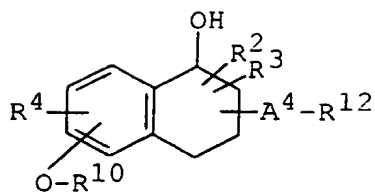


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(XV)
or a salt thereof

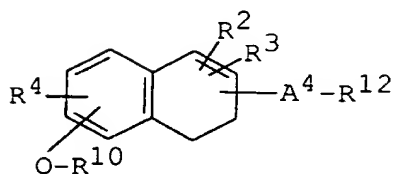
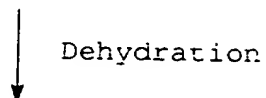
35

- 9 -

Process C

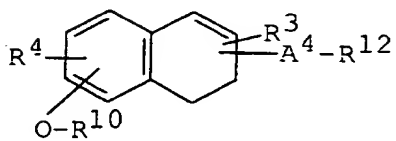
(XVI)
or a salt thereof

10



(XVII)
or a salt thereof

25 Process D



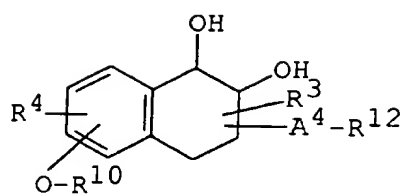
(XVIII)
or a salt thereof

35

- 10 -

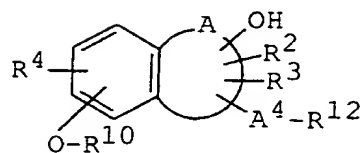


Oxydation



(XIX)
or a salt thereof

Process E



(XV)
or a salt thereof



Halogenation

5

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15

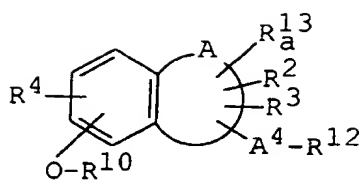
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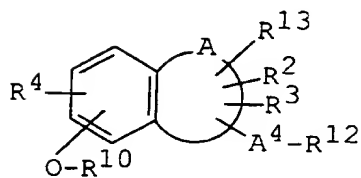
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- 11 -



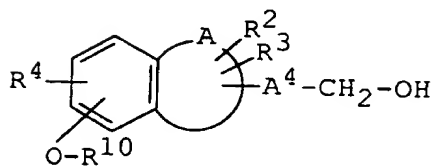
(XX)
or a salt thereof

Process F



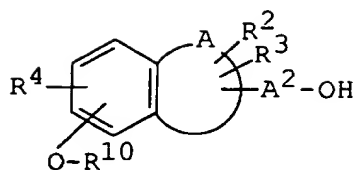
(XXI)
or a salt thereof

Reduction



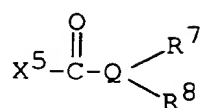
(XXII)
or a salt thereof

- 12 -

Process G

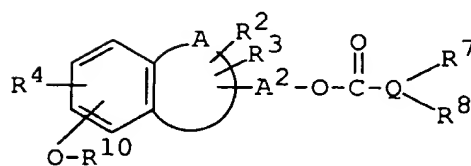
(XXIII)

or a salt thereof



(XXIV)

or a salt thereof

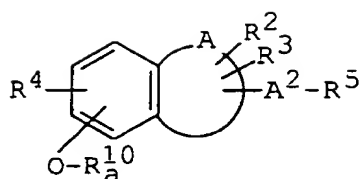


(XXV)

or a salt thereof

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Process H

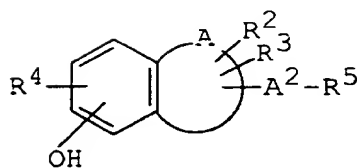
(XXXXIV)

or a salt thereof

15

Elimination reaction of the
hydroxy protective group

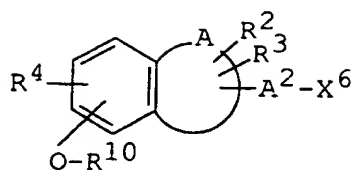
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(II)

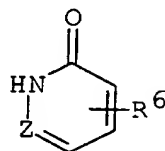
or a salt thereof

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Process I

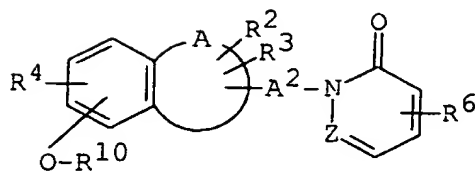
(XXVI)

or a salt thereof



(XXVII)

or a salt thereof

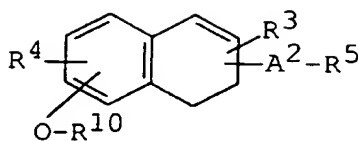


(XXVIII)

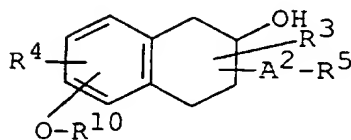
or a salt thereof

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- 15 -

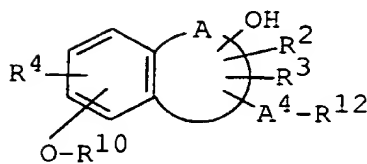
Process J

(XXIX)
or a salt thereof



20

(XXX)
or a salt thereof

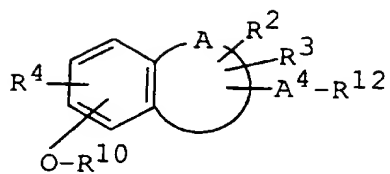
Process K

(XV)
or a salt thereof

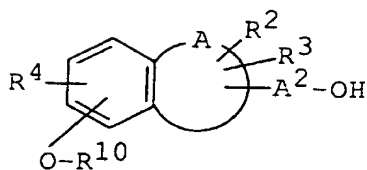
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- 16 -

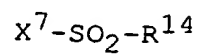
Reduction



(XXXI)
or a salt thereof

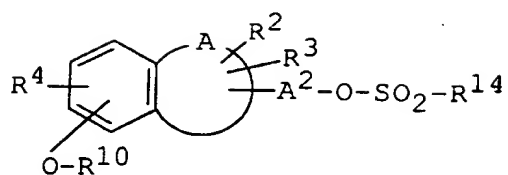
Process L

(XXIII)
or a salt thereof



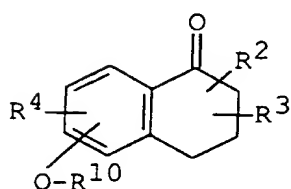
(XXXII)
or a salt thereof

- 17 -



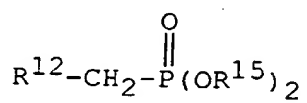
(XXXIII)
or a salt thereof

10 Process M



(XXXIV)
or a salt thereof

25



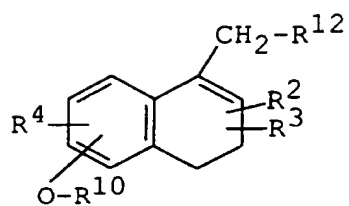
(XXXV)
or a salt thereof

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- 18 -

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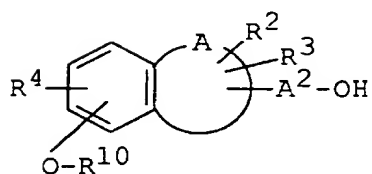
(XXXVI)

or a salt thereof

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Process N

15



(XXIII)

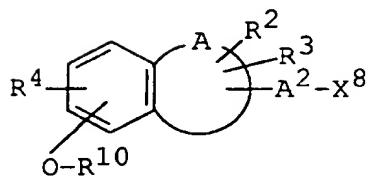
or a salt thereof

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Halogenation

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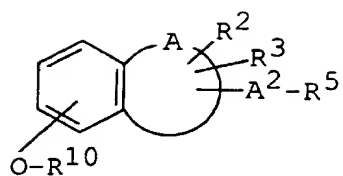


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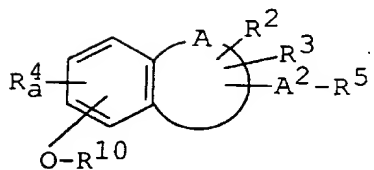
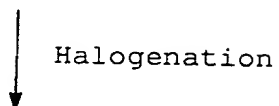
or a salt thereof

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- 19 -

Process 0

(XXXVII)
or a salt thereof



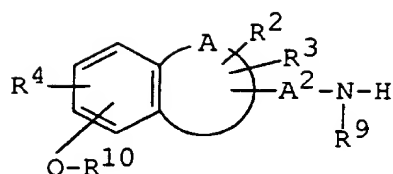
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(XXXVIII)
or a salt thereof

30

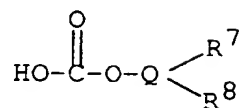
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- 20 -

Process P

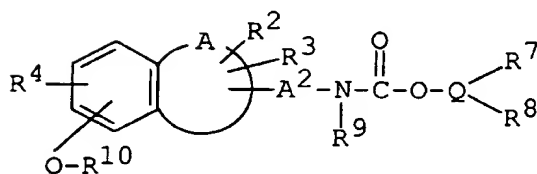
(XXXIX)

or a salt thereof



(IX)

or its reactive derivative
at the carboxy group
or a salt thereof

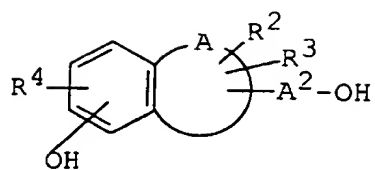


(XXXX)

or a salt thereof

35

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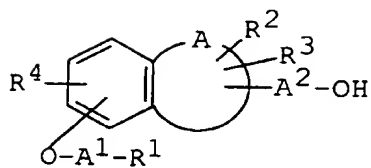
Process Q

(XXXI)
or a salt thereof

10

15

$X^1-A^1-R^1$
(III)
or a salt thereof

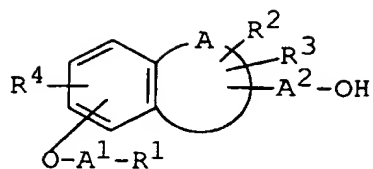


(IV)
or a salt thereof

30

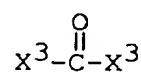
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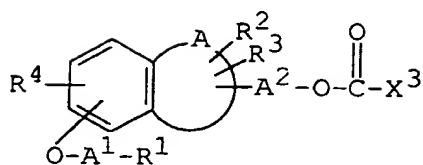
Process R

(IV)

or a salt thereof



(XXXXXII)



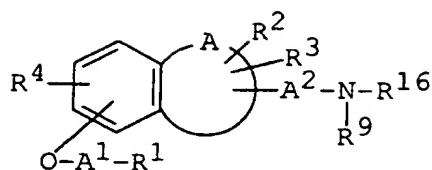
(VI)

or a salt thereof

30

35

- 23 -

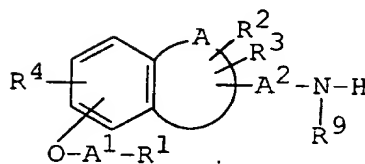
Process S

(XXXXIII)

or a salt thereof

15

Elimination reaction of
the amino protective group




(VIII)

or a salt thereof

25

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , A^1 , A^2 , Z , Q ,

30 X^1 , X^3 and  are each as defined above,

R^{10} is hydrogen or hydroxy protective group,

35 R^{11} is leaving group,

- 24 -

5 R^{12} is carboxy or protected carboxy,
 A^4 is bond or C_1-C_5 alkylene,
 R_a^{13} is halogen,
 R^{13} is hydrogen or halogen,
 X^5 is halogen,
 R_a^{10} is hydroxy protective group,
 X^6 is acid residue,
 X^7 is halogen,
10 R^{14} is lower alkyl, or aryl which may have
 suitable substituent(s),
 R^{15} is lower alkyl,
 X^8 is halogen,
 R_a^4 is halogen, and
 R^{16} is amino protective group.

15 Suitable pharmaceutically acceptable salts of the
 object compound (I) are conventional non-toxic salts and
 include a metal salt such as an alkali metal salt (e.g.
 sodium salt, potassium salt, etc.) and an alkaline earth
20 metal salt (e.g. calcium salt, magnesium salt, etc.), an
 ammonium salt, an organic base salt (e.g. trimethylamine
 salt, triethylamine salt, pyridine salt, picoline salt,
 dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt,
 etc.), an organic acid salt (e.g. acetate, maleate,
25 tartrate, methanesulfonate, benzenesulfonate, formate,
 toluenesulfonate, trifluoroacetate, etc.), an inorganic
 acid salt (e.g. hydrochloride, hydrobromide, sulfate,
 phosphate, etc.), a salt with an amino acid (e.g.
 arginine, aspartic acid, glutamic acid, etc.), and the
30 like.

 In the above and subsequent descriptions of the
 present specification, suitable examples and illustrations
 of the various definitions which the present invention
 include within the scope thereof are explained in detail
35 as follows.

- 25 -

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "aryl" and "aryl moiety" in the term "mono(or di or tri)aryl(lower)alkyl" may include phenyl, naphthyl and the like.

Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene or the like, preferably one having 1 to 3 carbon atom(s).

Suitable "C₁-C₅ alkylene" may include straight or branched one having 1 to 5 carbon atom(s), such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene or the like.

Suitable "lower alkyl" and "lower alkyl moiety" in the term "mono(or di or tri)aryl(lower)alkyl" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, t-pentyl, hexyl or the like, preferably one having 1 to 4 carbon atom(s).

Suitable "protected carboxy" may include esterified carboxy and the like.

Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxylethyl ester, 1(or 2 or 3)-acetoxypentyl ester, 1(or 2 or 3 or 4)-acetoxypentyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl

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ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-
pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester,
isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester,
3,3-dimethylbutyryloxymethyl ester, 1(or 2)-
5 pentanoyloxyethyl ester, etc.], lower
alkylsulfonyl(lower)alkyl ester (e.g. 2-mesyloethyl ester,
etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-
iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower
alkoxycarbonyloxy(lower)alkyl ester (e.g.
10 methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl
ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyl-
oxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.),
phthalidylidene(lower)alkyl ester, or (5-lower alkyl 2-
oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-
15 oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-
dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-
yl)ethyl ester, etc.];
lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.);
lower alkynyl ester (e.g. ethynyl ester, propynyl ester,
20 etc.);
ar(lower)alkyl ester which may have at least one suitable
substituent(s) such as mono(or di or tri)-
phenyl(lower)alkyl ester which may have at least one
suitable substituent(s) (e.g. benzyl ester,
25 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl
ester, trityl ester, benzhydryl ester,
bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester,
4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.);
aryl ester which may have at least one suitable
30 substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester,
tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl
ester, cumenyl ester, etc.);
phthalidyl ester; and the like.

Suitable "acid residue" may include halogen (e.g.
35 chlorine, bromine, iodine, etc.), sulfonyloxy (e.g.

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methysulfonyloxy, phenylsulfonyloxy, tolylsulfonyloxy, etc.), and the like.

Suitable "protected hydroxy" may include acyloxy and the like.

5 Suitable "acyl moiety" in the term "acyloxy" may include aliphatic acyl group and acyl group containing an aromatic or heterocyclic ring.

And, suitable examples of the said acyl may be lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, 10 isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);

lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, 15 butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);

lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); 20 arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.); aroyl (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indancarboxyl, etc.); ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.);

25 ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), and the like.

Suitable "halogen" may include chlorine, bromine, iodine and fluorine.

30 Suitable "leaving group" may include lower alkoxy (e.g., methoxy, ethoxy, propoxy, isopropoxy, butoxy, etc.) and the like.

Suitable "substituent" in the term "aryl which may have suitable substituent(s)" may include lower alkyl as 35 exemplified above, and the like.

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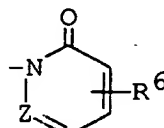
Suitable "amino protective group" may include acyl as exemplified above, mono(or di or tri)aryl(lower)alkyl and the like.

5 Suitable "hydroxy protective group" may include lower alkyl as exemplified above, silyl which may have one to three suitable substituent(s), and the like.

Suitable "substituent" in the term "silyl which may have one to three suitable substituent(s)" may include lower alkyl as exemplified above, aryl as exemplified
10 above, and the like.

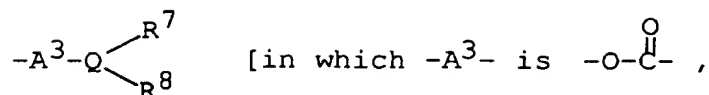
Preferred embodiments of the object compound (I) are as follows :

- 15 R^1 is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxy carbonyl),
 R^2 is hydrogen, hydroxy, or protected hydroxy (more preferably acyloxy),
 20 R^3 is hydrogen, hydroxy, protected hydroxy (more preferably acyloxy), lower alkyl or halogen,
 R^4 is hydrogen or halogen,
 A^1 is lower alkylene (more preferably C_1 - C_3 alkylene, most preferably methylene),
 25 A^2 is bond, or lower alkylene (more preferably C_1 - C_3 alkylene, most preferably methylene or ethylene),

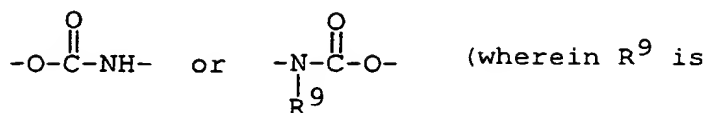
30 $-R^5$ is  [in which R^6 is diaryl(lower)alkyl

35 (more preferably diphenyl(lower)alkyl, most preferably diphenylmethyl), and Z is N or CH], or

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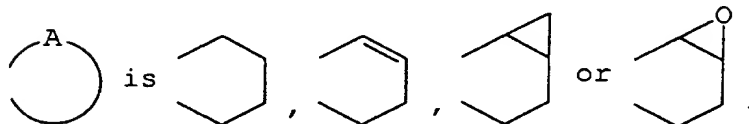
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10

hydrogen or lower alkyl), Q is N or CH,
 R^7 is aryl (more preferably phenyl), and R^8 is aryl
 (more preferably phenyl)], and

15



20

The processes for preparing the object and starting compounds of the present invention are explained in detail in the following.

25

Process 1

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

30

This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

35

The reaction temperature is not critical and the

- 30 -

reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of a base.

Suitable base may include the inorganic base such as
5 alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium
10 bicarbonate, potassium bicarbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.) or the like, and the organic base such as tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), di(lower)alkylaniline (e.g.
15 dimethylaniline, etc.), pyridine or the like.

Process 2

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to
20 elimination reaction of the carboxy protective group.

Suitable method of this reaction may include conventional one such as hydrolysis, reduction and the like.

25 (i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium,
30 potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

35 Suitable acid may include an organic acid [e.g.

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formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.]. The
5 elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such
10 as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, 1,2-dimethoxyethane, dioxane, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction
15 temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner,
20 including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid
25 (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g.
30 platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium
35 carbonate, etc.), nickel catalysts (e.g. reduced nickel,

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nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 3

The compound (Ic) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of a base.

Suitable base can be referred to that of Process 1. A liquid base can be also used as the solvent.

Process 4

The compound (Id) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

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This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of a base.

Suitable base can be referred to that of Process 1.

Process 5

The compound (Ie) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (IX) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (IX) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester,

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dimethyliminomethyl [$(\text{CH}_3)_2\text{N}^+=\text{CH}-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.), and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (IX) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (IX) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 6

The compound (Ig) or a salt thereof can be prepared

- 35 -

by reacting the compound (If) or a salt thereof with the compound (X) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Example 20 described later or
5 similar manners thereto.

Process A

The compound (XIII) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the
10 compound (XII) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparation 31 described later or similar manners thereto.

15 Process B

The compound (XV) or a salt thereof can be prepared by subjecting the compound (XIV) or a salt thereof to reduction reaction.

This reaction can be carried out in accordance with
20 the method disclosed in the Preparation 32 described later or similar manners thereto.

Process C

The compound (XVII) or a salt thereof can be prepared
25 by subjecting the compound (XVI) or a salt thereof to dehydration reaction.

This reaction can be carried out in accordance with the method disclosed in the Preparation 33 described later or similar manners thereto.

30

Process D

The compound (XIX) or a salt thereof can be prepared by subjecting the compound (XVIII) or a salt thereof to oxidation reaction.

35 This reaction can be carried out in accordance with

- 36 -

the methods disclosed in the Preparations 34 and 35 described later or similar manners thereto.

Process E

5 The compound (XX) or a salt thereof can be prepared by subjecting the compound (XV) or a salt thereof to halogenation reaction.

 This reaction can be carried out in accordance with the method disclosed in the Preparation 40-(1) described
10 later or similar manners thereto.

Process F

 The compound (XXII) or a salt thereof can be prepared by subjecting the compound (XXI) or a salt thereof to
15 reduction reaction.

 This reaction can be carried out in accordance with the methods disclosed in the Preparations 1, 11, 13 and 40-(2) described later or similar manners thereto.

20 Process G

 The compound (XXV) or a salt thereof can be prepared by reacting the compound (XXIII) or a salt thereof with the compound (XXIV) or a salt thereof.

 This reaction can be carried out in accordance with
25 the methods disclosed in the Preparations 2 and 46 described later or similar manners thereto.

Process H

 The compound (II) or a salt thereof can be prepared
30 by subjecting the compound (XXXXIV) or a salt thereof to elimination reaction of the hydroxy protective group.

 The reagent to be used in this reaction may include halotrialkylsilane (e.g., iodotrimethylsilane, etc.), alkali metal thioalkoxide (e.g., sodium thioethoxide, etc.),
35 alkali metal sulfide (e.g., sodium sulfide, etc.),

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alkali metal diphenylphosphide (e.g., lithium diphenylphosphide, etc.), aluminum halide (e.g., aluminum chloride, aluminum bromide, etc.), boron trihalide (e.g., boron trichloride, boron tribromide, etc.), pyridine hydrochloride, alkylmagnesium halide (e.g., methylmagnesium iodide, etc.), lithium halide (e.g., lithium chloride, etc.), tetraalkylammonium halide (e.g., tetrabutylammonium fluoride, etc.), a combination of methionine and sulfonic acid (e.g., methanesulfonic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol, (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

20

Process I

The compound (XXVIII) or a salt thereof can be prepared by reacting the compound (XXVI) or a salt thereof with the compound (XXVII) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparations 8, 17 and 19 described later or similar manners thereto.

The compound (XXVII) or a salt thereof can be prepared in accordance with the method disclosed in the Preparation 7 described later or similar manners thereto.

30

Process J

The compound (XXX) or a salt thereof can be prepared from the compound (XXIX) or a salt thereof in accordance with the method disclosed in the Preparation 54 described

35

- 38 -

later or similar manners thereto.

Process K

5 The compound (XXXI) or a salt thereof can be prepared by subjecting the compound (XV) or a salt thereof to reduction reaction.

This reduction can be carried out in a similar manner to that of the aforementioned Process 2, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 2.

Process L

15 The compound (XXXIII) or a salt thereof can be prepared by reacting the compound (XXIII) or a salt thereof with the compound (XXXII) or a salt thereof.

This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, pyridine, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

25 The reaction is usually carried out in the presence of a base.

Suitable base can be referred to that of Process 1.

Process M

30 The compound (XXXVI) or a salt thereof can be prepared by reacting the compound (XXXIV) or a salt thereof with the compound (XXXV) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparation 38 described later or similar manners thereto.

35

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Process N

The compound (XXXXV) or a salt thereof can be prepared by subjecting the compound (XXIII) or a salt thereof to halogenation reaction.

5 This reaction can be carried out in accordance with the methods disclosed in the Preparations 14 and 15 described later or similar manners thereto.

Process O

10 The compound (XXXVIII) or a salt thereof can be prepared by subjecting the compound (XXXVII) or a salt thereof to halogenation reaction.

 This reaction can be carried out in accordance with the method disclosed in the Preparation 21 described later
15 or similar manners thereto.

Process P

 The compound (XXXX) or a salt thereof can be prepared by reacting the compound (XXXIX) or a salt thereof with
20 the compound (IX) or its reactive derivative at the carboxy group or a salt thereof.

 This reaction can be carried out in a similar manner to that of the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g.
25 solvent, reaction temperature, etc.) can be referred to those of the Process 5.

Process Q

 The compound (IV) or a salt thereof can be prepared
30 by reacting the compound (XXXXI) or a salt thereof with the compound (III) or a salt thereof.

 This reaction can be carried out in a similar manner to that of the aforementioned Process 1, and therefore the reagents to be used and the reaction conditions (e.g.,
35 solvent, reaction temperature, etc.) can be referred to

- 40 -

those of the Process 1.

Process R

5 The compound (VI) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (XXXXII).

10 This reaction is usually carried out in a solvent such as acetonitrile, benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

15 The reaction is usually carried out in the presence of a base.

Suitable base can be referred to that of Process 1.

Process S

20 The compound (VIII) or a salt thereof can be prepared by subjecting the compound (XXXXIII) or a salt thereof to elimination reaction of the amino protective group.

25 This reaction can be carried out in a similar manner to that of the aforementioned Process 2, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 2.

30 The object compound (I) of this invention and pharmaceutically acceptable salt thereof have pharmacological activities such as an inhibitory activity on platelet aggregation, vasodilating activity, antihypertensive activity or the like and are prostaglandin I₂ agonists, and therefore can be used for treating and/or preventing arterial obstruction (e.g.,
35 chronic arterial obstruction, etc.), cerebrovascular

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disease, gastric ulcer, hepatitis, hepatic insufficiency, hepatic cirrhosis, arteriosclerosis, ischemic heart disease, restenosis after percutaneous transluminal coronary angioplasty, hypertension, inflammation, heart failure, renal disease (e.g., renal failure, nephritis, etc.), diabetic complication (e.g., diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, etc.), peripheral circulatory disturbance, and the like, and can be also used for protecting organs after transplantation.

10

In order to show the utility of the object compound (I), pharmacological data of the representative compounds thereof are shown in the following.

- 15 i) Inhibition of human platelet aggregation induced by ADP

[I] Test Compound :

- 20 (1) Sodium salt of [5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
- (2) 2-[(1,2,3,4-Tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone

25

[II] Test Method :

Human blood was obtained from healthy volunteers and mixed with 1/10 volume of 3.8% sodium citrate, pH 7.4.

30 The citrate blood was centrifuged at 150 X g for 10 minutes and the platelet rich plasma (PRP) was removed. The remaining blood was centrifuged for a further 10 minutes at 1500 X g to prepare the platelet poor plasma

35

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(PPP), which was used as a reference for platelet aggregation. Aggregation studies were carried out using HEMATRACER 801 (NBS, Japan), a 8 channel aggregometer. 25 μ l of sample solution and 225 μ l of PRP were mixed and stirred at 1000 rpm for 2 minutes at 37°C. Aggregation was induced by ADP solution at the final concentration of 2.5 μ M.

[III] Test result :

Test compound	Inhibition (%)
(1) (1.0×10^{-7} M)	97 ± 1.2
(2) (1.0×10^{-6} M)	100 ± 0.4

mean \pm S.E.

ii) Effect on mean arterial blood pressure in conscious rats

[I] Test Compound :

Sodium salt of [5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate

[II] Test Method :

Male Sprague-Dawley rats, aged 8-9 weeks, were anesthetized with ether. A polyethylene cannula filled with heparin solution was inserted into the femoral artery of the rats to measure mean blood pressure. Mean blood pressure was measured with a pressure transducer and recorded on a polygraph. The test compound dissolved in

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ethanol, polyethylene glycol and distilled water (1:1:1) was administered through a polyethylene cannula inserted into the femoral vein in a volume of 1 ml/kg. Intravenous hypotensive effect of the test compound was expressed as the maximal decrease (R max). Briefly, R max was expressed as maximal Δ change compared to mean blood pressure prior to the administration of the test compound.

[III] Test Result :

Test compound	R max (%)
10 mg/kg	27.5

iii) Receptor binding assay

[I] Test Compound :

Sodium salt of (2R)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate

[II] Test Method :

cDNA of human IP receptor was cloned and expressed in COS7 using pCDM8 vector in a similar manner to that described in the literatures [J. Biol. Chem., Vol. 269, No. 16, pp.12173-12178 (1994) : Circulation, Vol. 90, No. 4, pp1643-1647 (1994) : FEBS Letters 344 (1994) 74-78].

After transfection, cells which expressed human IP receptor were collected with cell scraper at 4°C and stored in -80°C.

The composition of assay buffer was as follows : 20 mM MES (pH 6.0), 10 mM MgCl₂, 1 mM EDTA, and 0.1 mM PMSF. Frozen cells were thawed and aliquots (4.5 x 10⁵ cells)

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were incubated for 60 minutes under shaking at 30°C in plastic tubes in 100 µl of assay buffer with 10 nM of [³H]-iloprost in the presence or absence of the test compound (1×10^{-6} M).

5 To determine the non-specific binding, iloprost at 10 µM was added. Each assay was preformed in duplicate. Reaction mixture was filtered through a Whatman GF/C glass filter to stop the reaction. After washing the filter with ice-cold assay buffer, the radioactivity of the
10 filter was countered. Non-specific binding was subtracted from total binding to yield specific binding. The effect of the test compound was expressed as % inhibition of specific [³H]-iloprost binding.

15 [III] Test Result :

Inhibition (%) : 96.5

20 The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form (e.g. tablet, pellet, troche, capsule, suppository, cream, ointment, aerosol, powder, solution, emulsion, suspension etc.), which contains the object compound (I)
25 or a pharmaceutically acceptable salt thereof as an active ingredient, suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation.

30 The pharmaceutical composition of this invention can contain various organic or inorganic carrier materials, which are conventionally used for pharmaceutical purpose, such as excipient (e.g. sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate,
35 calcium carbonate, etc.), binding agent (e.g. cellulose,

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methyl cellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethyleneglycol, sucrose, starch, etc.), disintegrator (e.g. starch, carboxymethyl cellulose, calcium salt of carboxymethyl cellulose, hydroxypropylstarch, sodium glycol-starch, sodium bicarbonate, calcium phosphate, calcium citrate, etc.), lubricant (e.g. magnesium stearate, talc, sodium laurylsulfate, etc.), flavoring agent (e.g. citric acid, mentol, glycine, orange powders, etc.), preservative (e.g. sodium benzoate, sodium bisulfite, methylparaben, propylparaben, etc.), stabilizer (e.g. citric acid, sodium citrate, acetic acid, etc.), suspending agent (e.g. methyl cellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agent, aqueous diluting agent (e.g. water), base wax (e.g. cacao butter, polyethyleneglycol, white petrolatum, etc.).

The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight, conditions of the patient or the administering method.

The following preparations and examples are given only for the purpose of illustrating the present invention in more detail.

Preparation 1

A suspension of ethyl (5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)acetate (1.02 g) and lithium aluminum hydride (0.20 g) in tetrahydrofuran (15 ml) was stirred at 0°C for 2.5 hours. The solution was poured into cold 1N-hydrochloric acid, then the resulting mixture was filtered through the celite, and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo to afford 2-(5-methoxy-1,2,3,4-

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tetrahydro-1-naphthyl)ethanol as a colorless oil (0.85 g).

NMR (CDCl₃, δ) : 1.66-2.07 (7H, m), 2.49-2.76 (2H, m), 2.92-2.99 (1H, m), 3.77 (2H, t, J=6.8Hz), 3.81 (3H, s), 6.67 (1H, d, J=8.0Hz), 6.81 (1H, d, J=7.7Hz), 7.11 (1H, dd, J=8.0, 7.7Hz)

(+) APCI MS m/z : 207 (M⁺+1)

Preparation 2

A mixture of (1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methanol (192 mg) and N,N-diphenylcarbonyl chloride (348 mg) in pyridine (180 mg) was stirred at 100°C for 2 hours, cooled to room temperature, and partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed successively with brine, aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was triturated with diethyl ether to afford (1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methyl N,N-diphenylcarbamate (218 mg) as a pale purple powder.

mp : 143.5-146°C

IR (Nujol) : 1710, 1260 cm⁻¹

NMR (CDCl₃, δ) : 1.22-1.43 (1H, m), 1.8-2.05 (2H, m), 2.35-2.6 (2H, m), 2.65-2.9 (2H, m), 3.80 (3H, s), 4.06-4.23 (2H, m), 6.65 (1H, d, J=7.9Hz), 6.65 (1H, d, J=7.9Hz), 7.11 (1H, t, J=7.9Hz), 7.16-7.38 (10H, m)

(+) APCI MS m/z : 388 (M⁺+1)

Preparation 3

The following compound was obtained according to a similar manner to that of Preparation 2.

2-(5-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl N,N-diphenylcarbamate

mp : 97°C

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IR (Nujol) : 1710 cm^{-1}

NMR (CDCl_3 , δ) : 1.68-2.01 (6H, m), 2.46-2.74 (3H, m), 3.79 (3H, s), 4.26 (2H, t, $J=6.4\text{Hz}$), 6.58 (1H, d, $J=7.7\text{Hz}$), 6.64 (1H, d, $J=8.0\text{Hz}$), 7.05 (1H, dd, $J=8.0, 7.7\text{Hz}$), 7.16-7.38 (10H, m)

5 (+) APCI MS m/z : 402 (M^++1)Preparation 4

10 A suspension of (1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methyl N,N-diphenylcarbamate (1.93 g) and DL-methionine (7.43 g) in methanesulfonic acid (47.9 ml) was stirred at room temperature for 22 hours, then poured into ice water. The resulting mixture was extracted with ethyl acetate. The extract was washed successively with brine 15 (twice), aqueous sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford (1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl N,N-diphenylcarbamate (82 mg) as yellow 20 solids.

mp : 96-98°C

IR (Nujol) : 3330, 1675, 1585 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.25-1.47 (1H, m), 1.85-2.05 (2H, m), 2.42-2.59 (2H, m), 2.66-2.84 (2H, m), 4.07-4.23 (2H, m), 5.05 (1H, s), 6.58 (1H, d, $J=7.7\text{Hz}$), 6.62 (1H, d, $J=7.7\text{Hz}$), 6.96 (1H, t, $J=7.7\text{Hz}$), 7.15-7.68 (10H, m)

30 (+) APCI MS m/z : 374 (M^++1)Elemental Analysis Calcd. for $\text{C}_{24}\text{H}_{23}\text{NO}_3$:

35 C 77.19, H 6.21, N 3.75
Found : C 77.31, H 6.29, N 3.67

Preparation 5

35 A suspension of 2-(5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl N,N-diphenylcarbamate (0.93 g) and DL-

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methionine (3.50 g) in methanesulfonic acid (15 ml) was stirred at room temperature for 16 hours, then poured into ice water. The resulting mixture was extracted with ethyl acetate. The extract was washed successively with 5% hydrochloric acid and brine, dried over sodium sulfate, and evaporated in vacuo to afford crude 2-(5-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl N,N-diphenylcarbamate (0.77 g).

10 Example 1

A suspension of (1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl N,N-diphenylcarbamate (67 mg), ethyl bromoacetate (33 mg) and potassium carbonate (37 mg) in N,N-dimethylformamide (1.0 ml) was stirred at room temperature for 5.5 hours and then extracted with ethyl acetate. The extract was washed with water and brine (twice), dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford [5-(ethoxycarbonylmethoxy)-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (61 mg) as an oil.

IR (Film) : 1755, 1710, 1585, 1200 cm^{-1}

(+) APCI MS m/z : 460 ($M^+ + 1$)

25 Example 2

The following compound was obtained according to a similar manner to that of Example 1.

2-[5-(Ethoxycarbonylmethoxy)-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate

IR (Film) : 1760-1700 (broad) cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7.1\text{Hz}$), 1.57-2.00 (6H, m), 2.48-2.76 (3H, m), 4.18-4.31 (4H, m), 4.60 (2H, s), 6.50 (1H, d, $J=8.0\text{Hz}$), 6.61 (1H, d, $J=7.7\text{Hz}$), 7.01 (1H, dd, $J=8.0, 7.7\text{Hz}$),

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7.05-7.38 (10H, m)

(+) APCI MS m/z : 474 ($M^+ + 1$)Example 3

5. A solution of [5-(ethoxycarbonylmethoxy)-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (59 mg) and 1N sodium hydroxide solution (0.15 ml) in ethanol (1.5 ml) was stirred at room temperature for 1 hour and neutralized with 1N hydrochloric acid (0.15 ml), then
10 extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was powdered from n-hexane to afford [5-(carboxymethoxy)-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (47 mg) as a colorless powder.

15 mp : 137-141.5°C

IR (Nujol) : 1740, 1705, 1580, 1250 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.2-1.35 (1H, m), 1.75-2.0 (2H, m), 2.27-2.83 (4H, m), 4.06 (2H, br d, $J=5.8\text{Hz}$),
4.64 (2H, s), 6.59 (1H, d, $J=7.8\text{Hz}$), 6.63 (1H, d, $J=7.8\text{Hz}$), 7.01 (1H, t, $J=7.8\text{Hz}$), 7.23-7.43
20 (10H, m), 12.95 (1H, br s)

(+) APCI MS m/z : 432 ($M^+ + 1$)Example 4

25 A solution of 2-[5-(ethoxycarbonylmethoxy)-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate (0.83 g) and 1N sodium hydroxide solution (2.1 ml) in dioxane (5 ml) was stirred at room temperature for 30 minutes and washed with ether. The resulting aqueous layer was
30 acidified with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was powdered from 2-propanol to afford 2-[5-(carboxymethoxy)-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate (0.46 g) as a colorless powder.
35

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mp : 145°C

IR (Nujol) : 1730, 1695 cm⁻¹

NMR (DMSO-d₆, δ) : 1.60-1.91 (6H, m), 2.42-2.60 (3H, m), 3.57 (1H, broad), 4.15 (2H, t, J=6.2Hz), 4.61 (2H, s), 6.54 (1H, d, J=7.7Hz), 6.57 (1H, d, J=8.1Hz), 6.99 (1H, dd, J=8.1, 7.7Hz), 7.20-7.41 (10H, m)

5 (+) APCI MS m/z : 446 (M⁺+1)10 Example 5

A solution of 2-[5-(carboxymethoxy)-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate (0.12 g) and 1N-sodium hydroxide solution (0.265 ml) in ethanol was evaporated in vacuo. The residue was powdered from ethanol to afford sodium salt of 2-[5-(carboxymethoxy)-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate (0.11 g) as a colorless powder.

15 mp : 200-215°C

IR (Nujol) : 1700, 1610 cm⁻¹

20 NMR (CD₃OD, δ) : 1.67-2.01 (6H, m), 2.57-2.85 (3H, m), 4.18-4.26 (2H, m), 4.35 (2H, s), 6.49 (1H, d, J=7.7Hz), 6.56 (1H, d, J=8.1Hz), 6.94 (1H, dd, J=8.1, 7.7Hz), 7.20-7.40 (10H, m)

FAB MS m/z : 468 (M⁺)

25

Example 6

To a solution of [5-(ethoxycarbonylmethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (570 mg) in ethanol (20 ml) was added 1N-sodium hydroxide solution (1.2 ml). After stirring for 4 hours at room temperature, the solvent was removed in vacuo to give sodium salt of [5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (500 mg).

35 IR (Nujol) : 3300-3400, 1700, 1580 cm⁻¹

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NMR (D_2O , δ) : 1.2-1.6 (2H, m), 2.1-2.6 (4H, m),
3.72 (1H, d, $J=11.0\text{Hz}$), 3.85 (1H, d, $J=11.0\text{Hz}$),
4.13 (2H, s), 6.29 (2H, m), 6.4-7.0 (12H, m)
FAB MS m/z : 470 (M^++1)

5

Preparation 6

To a solution of (5-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methanol (1.00 g) in dry pyridine (10 ml) was added p-toluenesulfonyl chloride (1.15 g) under ice bath cooling. The mixture was stirred for 1 day at room temperature and partitioned between ethyl acetate and water. The organic layer was separated, washed with water (twice), 1N hydrochloric acid and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 10:1) to give (5-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methyl p-toluenesulfonate (1.70 g) as a white powder.

mp : 81-82°C
IR (Nujol) : 1590, 1370, 1260, 1180, 790, 770,
720 cm^{-1}

MASS (+ APCI) : 347 (M^++1)
NMR ($CDCl_3$, δ) : 1.10-1.50 (1H, m), 1.80-2.20 (2H, m), 2.20-2.60 (2H, m), 2.45 (3H, s), 2.60-2.95 (2H, m), 3.79 (3H, s), 3.99 (2H, d, $J=6.6\text{Hz}$), 6.64 (1H, d, $J=7.9\text{Hz}$), 6.64 (1H, d, $J=7.9\text{Hz}$), 7.07 (1H, dd, $J=7.9\text{Hz}$, 7.9Hz), 7.34 (2H, d, $J=8.2\text{Hz}$), 7.79 (2H, d, $J=8.2\text{Hz}$)

30 Preparation 7

A solution of 1,1-diphenylacetone (25 g) and glyoxylic acid monohydrate (41.6 g) in 1,2-dimethoxyethane (75 ml) was refluxed for 3 days. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water (twice) and evaporated in

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vacuo. The residue was partitioned between ethyl acetate and ammonia solution (200 ml) and the aqueous layer was separated. To the aqueous layer was added hydrazine hydrate (22.6 g) and the mixture was stirred for 2 hours at 100°C. After being cooled, the reaction mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated in vacuo. The residue was recrystallized from ethyl acetate to give 6-diphenylmethyl-3(2H)-pyridazinone (6.26 g) as a white powder.

mp : 161-162°C

IR (Nujol) : 3300-2800, 1660, 1600, 760, 740, 700 cm⁻¹

NMR (CDCl₃, δ) : 5.44 (1H, s), 6.88 (1H, d, J=9.8Hz), 7.10-7.40 (11H, m), 11.29 (1H, br s)

MASS (+ APCI) : 263 (M⁺+1)

Elemental Analysis Calcd. for C₁₇H₁₄N₂O :

C 77.84, H 5.38, N 10.68

Found : C 77.76, H 5.39, N 10.66

Preparation 8

A suspension of 6-diphenylmethyl-3(2H)-pyridazinone (0.58 g) and sodium hydride (60%, 110 mg) in dry N,N-dimethylformamide (7 ml) was stirred at 0°C for 30 minutes. A solution of (5-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methyl p-toluenesulfonate (0.77 g) in dry N,N-dimethylformamide (5 ml) was added dropwise to the suspension at room temperature. The mixture was stirred for 6 hours and poured into ice-1N hydrochloric acid and extracted with ethyl acetate. The extract was separated, washed with water (twice) and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane: ethyl acetate = 5:1-3:1) to give 2-[(1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-

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pyridazinone (0.61 g) as a pale yellow oil.

IR (Film) : 1660, 1590, 770, 730, 700 cm^{-1}

NMR (CDCl_3 , δ) : 1.35-1.55 (1H, m), 1.80-2.00 (1H, m), 2.25-3.00 (5H, m), 3.80 (3H, s), 4.05-4.25 (2H, m), 5.45 (1H, s), 6.61 (1H, d, $J=6.9\text{Hz}$), 6.64 (1H, d, $J=6.9\text{Hz}$), 6.87 (1H, d, $J=9.5\text{Hz}$), 7.00-7.35 (12H, m)

MASS (+ APCI) : 437 (M^++1)

10 Preparation 9

To a solution of 2-[(1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.60 g) in dry dichloromethane (5 ml) was added dropwise 1N boron tribromide in dichloromethane (1.5 ml) under ice bath cooling. The mixture was stirred at the same temperature for 2.5 hours. The mixture was poured into 1N hydrochloric acid and extracted with ethyl acetate. The extract was separated, washed with brine, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane: ethyl acetate = 1:1) to give 2-[(1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.44 g) as a pale yellow oil.

IR (Film) : 3000-3500, 1650, 770, 700 cm^{-1}

NMR (CDCl_3 , δ) : 1.35-1.66 (1H, m), 1.80-2.00 (1H, m), 2.25-2.90 (5H, m), 4.00-4.30 (2H, m), 5.47 (1H, s), 6.55-6.65 (2H, m), 6.90-7.35 (14H, m)

MASS (+ APCI) : 423 (M^++1)

30 Example 7

A suspension of 2-[(1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (425 mg), ethyl bromoacetate (184 mg) and potassium carbonate (152.9 mg) in acetonitrile (15 ml) was refluxed for 6 hours. After cooling, the precipitated solid was filtered

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off and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 1:1) to give 2-[(1,2,3,4-tetrahydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.43 g) as pale yellow oil.

IR (Film) : 1750, 1660, 1580, 760, 720, 700 cm^{-1}

NMR (CDCl_3 , δ) : 1.35-1.60 (1H, m), 1.29 (3H, t, $J=7.1\text{Hz}$), 1.80-2.00 (1H, m), 2.20-3.20 (5H, m), 4.15-4.20 (2H, m), 4.25 (2H, q, $J=7.1\text{Hz}$), 4.61 (2H, s), 5.45 (1H, s), 6.51 (1H, d, $J=7.8\text{Hz}$), 6.64 (1H, d, $J=7.8\text{Hz}$), 6.86 (1H, d, $J=9.5\text{Hz}$), 7.08 (1H, dd, $J=7.8\text{Hz}$, 7.8Hz), 7.10-7.35 (11H, m)

MASS (+ APCI) : 509 (M^++1)

Example 8

A solution of 2-[(1,2,3,4-tetrahydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.43 g) in 1,2-dimethoxyethane (9.0 ml) and 1.0N aqueous solution of sodium hydroxide (0.85 ml) was stirred at room temperature for 5 hours. The solution was evaporated in vacuo and extracted with ethyl acetate and 1N hydrochloric acid. The organic layer was separated and washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was crystallized from n-hexane, ethyl acetate and ether to give 2-[(1,2,3,4-tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (330 mg) as a white powder.

mp : 176-178°C

IR (Nujol) : 2600-2200, 1740, 1640, 770, 700 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 1.20-1.45 (1H, m), 1.70-1.90 (1H, m), 2.10-2.90 (5H, m), 3.90-4.10 (2H, m), 4.65 (2H, s), 5.57 (1H, s), 6.55-6.65 (2H, m),

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6.90-7.05 (2H, m), 7.20-7.35 (11H, m), 12.96
(1H, br s)

MASS (+ APCI) : 481 ($M^+ + 1$)

5 Preparation 10

A mixture of (1R,2S)-methyl [1-hydroxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthyl]formate (2.22 g) and 10% palladium on carbon in methanol (50 ml) was stirred under hydrogen (2-3 atm) at room temperature for 22 hours. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 4:1) to give (S)-methyl (5-methoxy-1,2,3,4-tetrahydro-2-naphthyl)formate as a colorless oil (1.66 g).

15 NMR ($CDCl_3$, δ) : 1.70-1.90 (1H, m), 2.15-2.30 (1H, m), 2.50-3.00 (5H, m), 3.74 (3H, s), 3.81 (3H, s), 6.60-6.75 (2H, m), 7.05-7.15 (1H, m)

MASS (+ APCI) : 221 ($M^+ + 1$)

20 Preparation 11

To a mixture of lithium aluminum hydride (0.28 g) in dry tetrahydrofuran (THF) (5 ml) was added dropwise a solution of (S)-methyl [5-methoxy-1,2,3,4-tetrahydro-2-naphthyl]formate (1.65 g) in THF (7 ml) at -60°C under nitrogen. After 1 hour, a mixture of 1N hydrochloric acid solution (5 ml) and THF (5 ml) was added dropwise to the reaction mixture at -60°C. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with 1N hydrochloric acid solution, sodium hydrogencarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo to give (5-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methanol as a white powder (1.23 g).

30 $[\alpha]_D^{30} = -71.98^\circ$ (C=1.26, CH_2Cl_2)

35 NMR ($CDCl_3$, δ) : 1.25-2.20 (4H, m), 2.40-2.65 (2H,

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m), 2.80-3.00 (2H, m), 3.62 (2H, d, J=6.3Hz),
3.81 (3H, s), 6.66 (1H, d, J=7.9Hz), 6.72 (1H,
d, J=7.9Hz), 7.08 (1H, dd, J=7.9Hz, 7.9Hz)

5 Preparation 12

The following compound was obtained according to a
similar manner to that of Preparation 6.

10 (S)-(5-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)methyl
methanesulfonate

$[\alpha]_D^{25} = -45.70^\circ$ (C=1.00, CH₂Cl₂)

IR (Film) : 1580, 1340, 1170 cm⁻¹

15 NMR (CDCl₃, δ) : 1.30-1.60 (1H, m), 1.90-2.30 (2H,
m), 2.45-2.70 (2H, m), 2.80-3.00 (2H, m), 3.03
(3H, s), 3.81 (3H, s), 4.20 (2H, d, J=6.5Hz),
6.60-6.75 (2H, m), 7.00-7.25 (1H, m)

MASS (+ APCI) : 271 (M⁺+1)

Preparation 13

20 To a solution of methyl (5-methoxy-3,4-dihydro-2-
naphthyl)formate (0.75 g) in toluene (10 ml) was added
dropwise a solution of diisobutylaluminum hydride [1.02N
in toluene (6.7 ml)] at 4°C-6°C under nitrogen atmosphere.
The reaction mixture was stirred under same conditions for
25 2.5 hours. The mixture was poured into a saturated
ammonium chloride solution, and the organic layer was
separated, washed with brine, dried over magnesium
sulfate, and evaporated in vacuo to give crude (5-methoxy-
3,4-dihydro-2-naphthyl)methanol as a colorless oil (0.66
30 g).

IR (Film) : 3700-3100, 1600, 1580 cm⁻¹

35 NMR (CDCl₃, δ) : 2.28 (2H, t, J=8.5Hz), 2.85 (2H, t,
J=8.5Hz), 3.83 (3H, s), 4.22 (2H, d, J=4.7Hz),
6.42 (1H, t, J=1.5Hz), 6.60-6.80 (2H, m),
7.05-7.15 (1H, m)

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MASS (+ APCI) : 173 ($M^+ + 1 - H_2O$)Preparation 14

Carbontetrabromide (1.00 g x 4) was added portionwise
5 to a solution of 3,4-dihydro-5-methoxy-2-naphthyl)methanol
(2.00 g) and triphenylphosphine (4.14 g) in
dichloromethane (40 ml) at room temperature. The reaction
mixture was stirred for 2 days and evaporated in vacuo.
Hexane and diethyl ether were added to the residue and
10 white powder was filtered off and the filtrate was
evaporated in vacuo to give crude 3-bromomethyl-1,2-
dihydro-8-methoxynaphthalene as a pale yellow oil.

Preparation 15

15 To a solution of 2-(5-methoxy-1,2,3,4-tetrahydro-1-
naphthyl)ethanol (0.20 g) and triphenylphosphine (0.42 g)
in dichloromethane (10 ml) was added tetrabromomethane
(0.90 g) at 5°C. The solution was stirred at 5°C for 1.5
hours and evaporated in vacuo. To the residue, ethyl
20 acetate was added and the insoluble material was filtered
off. The ethyl acetate solution was evaporated in vacuo.
The residue was chromatographed (n-hexane) over silica gel
to afford 2-(5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl
bromide (0.18 g) as a colorless oil.

25 NMR ($CDCl_3$, δ) : 1.64-1.85 (4H, m), 2.03-2.29 (2H,
m), 2.57-2.76 (2H, m), 2.98-3.02 (1H, m), 3.45-
3.60 (2H, m), 3.81 (3H, s), 6.68 (1H, d,
J=7.9Hz), 6.80 (1H, d, J=7.9Hz), 7.20 (1H, dd,
J=7.9, 7.9Hz)

30 MASS (APCI) m/z : 269, 271 ($M^+ + 1$)

Preparation 16

(S)-2-[(1,2,3,4-Tetrahydro-5-methoxy-2-
naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone was
35 prepared from (S)-(5-methoxy-1,2,3,4-tetrahydro-2-

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naphthyl)methyl methanesulfonate in a similar manner to that of Preparation 8.

$$[\alpha]_D^{30} = -29.76^\circ \text{ (C=0.86, CH}_2\text{Cl}_2\text{)}$$

NMR (CDCl₃, δ) : 1.35-1.55 (1H, m), 1.80-2.00 (1H, m), 2.25-3.00 (5H, m), 3.80 (3H, s), 4.05-4.25 (2H, m), 5.45 (1H, s), 6.61 (1H, d, J=6.9Hz), 6.64 (1H, d, J=6.9Hz), 6.87 (1H, d, J=9.5Hz), 7.00-7.35 (12H, m)

MASS (+ APCI) : 437 (M⁺+1)

Preparation 17

To a solution of potassium tert-butoxide (0.39 g) and 18-crown-6 (0.08 g) in dry N,N-dimethylformamide (4 ml) was added 6-diphenylmethyl-3(2H)-pyridazinone (0.83 g) at room temperature. After ten minutes, 3-bromomethyl-1,2-dihydro-8-methoxynaphthalene (0.80 g) was added to the solution and stirred at the same temperature overnight. The reaction mixture was poured into ethyl acetate and 1N hydrochloric acid and the organic layer was separated, washed with water, aqueous sodium hydrogencarbonate solution and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 1:1) to give 2-[(3,4-dihydro-5-methoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.55 g).

IR (CH₂Cl₂) : 1670, 1600 cm⁻¹

NMR (CDCl₃, δ) : 2.22 (2H, t, J=8.0Hz), 2.77 (2H, t, J=8.0Hz), 3.82 (3H, s), 4.84 (2H, s), 5.44 (1H, s), 6.26 (1H, s), 6.22 (1H, d, J=8.3Hz), 6.73 (1H, d, J=7.5Hz), 6.86 (1H, d, J=9.6Hz), 7.00-7.33 (12H, m)

MASS (+ APCI) : 435 (M⁺+1)

Preparation 18

The following compounds were obtained according to a

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similar manner to that of Preparation 17.

(1) 1-[(3,4-Dihydro-5-methoxy-2-naphthyl)methyl]-5-diphenylmethyl-2(1H)-pyridone

5 IR (CH₂Cl₂) : 1670, 1600 cm⁻¹

NMR (CDCl₃, δ) : 2.16 (2H, t, J=8.2Hz), 2.75 (2H, t, J=8.2Hz), 3.83 (3H, s), 4.62 (2H, s), 5.23 (1H, s), 6.15 (1H, s), 6.55-6.60 (2H, m), 6.70-6.85 (2H, m), 7.05-7.35 (12H, m)

10 MASS (+ APCI) : 434 (M⁺+1)

(2) 1-[(3,4-Dihydro-5-methoxy-2-naphthyl)methyl]-3-diphenylmethyl-2(1H)-pyridone

IR (CH₂Cl₂) : 1650, 1600 cm⁻¹

15 NMR (CDCl₃, δ) : 2.18 (2H, t, J=8.2Hz), 2.79 (2H, t, J=8.2Hz), 3.81 (3H, s), 4.71 (2H, s), 5.82 (1H, s), 6.11 (1H, t, J=6.8Hz), 6.24 (1H, s), 6.60-6.90 (3H, m), 7.05-7.35 (12H, m)

MASS (+ APCI) : 434 (M⁺+1)

20

Preparation 19

To a solution of 6-diphenylmethyl-3(2H)-pyridazinone (0.22 g) and potassium tert-butoxide (0.10 g) in N,N-dimethylformamide (2 ml) was added a solution of 2-(5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl bromide (0.18 g) in N,N-dimethylformamide (3 ml) at room temperature. The reaction mixture was stirred for 2 hours at the same temperature and partitioned between water and ethyl acetate. The organic layer was washed with water (3 times) and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane - ethyl acetate) over silica gel to afford 2-[2-(5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.25 g) as an oil.

35 NMR (CDCl₃, δ) : 1.65-2.05 (4H, m), 2.10-2.28 (1H,

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m), 2.50-2.85 (3H, m), 3.80 (3H, s), 4.07-4.33 (3H, m), 5.46 (1H, s), 6.64 (1H, d, J=8.5Hz), 6.69 (1H, d, J=9.4Hz), 6.84 (1H, d, J=9.4Hz), 7.02-7.36 (12H, m)

5 MASS (APCI) (m/z) : 451 (M⁺+1)

Preparation 20

The following compounds were obtained according to a similar manner to that of Preparation 9.

10

(1) (S)-2-[(1,2,3,4-Tetrahydro-5-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
[α]_D²⁵ = -30.28° (C=1.04, CH₂Cl₂)

IR (Film) : 3500-3000, 1650, 770, 700 cm⁻¹

15 NMR (CDCl₃, δ) : 1.35-1.60 (1H, m), 1.80-2.00 (1H, m), 2.25-2.90 (5H, m), 4.00-4.30 (2H, m), 5.47 (1H, s), 6.55-6.65 (2H, m), 6.90-7.35 (14H, m)

MASS (+ APCI) : 423 (M⁺+1)

20

(2) 2-[(3,4-Dihydro-5-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone

mp : 174-176°C

IR (Nujol) : 3200, 1650 cm⁻¹

25 NMR (DMSO-d₆, δ) : 2.09 (2H, t, J=8.2Hz), 2.62 (2H, t, J=8.2Hz), 4.72 (2H, s), 5.56 (1H, s), 6.09 (1H, s), 6.45 (1H, d, J=7.2Hz), 6.65 (1H, d, J=7.2Hz), 6.85-6.95 (2H, m), 7.15-7.40 (11H, m), 9.23 (1H, s)

MASS (+ APCI) : 421 (M⁺+1)

30

(3) 1-[(3,4-Dihydro-5-hydroxy-2-naphthyl)methyl]-5-diphenylmethyl-2(1H)-pyridone

mp : 178-180°C

IR (Nujol) : 3150, 1650 cm⁻¹

35 NMR (CDCl₃, δ) : 2.15 (2H, t, J=8.2Hz), 2.70 (2H, t,

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J=8.2Hz), 4.62 (2H, s), 5.26 (1H, s), 6.11 (1H, s), 6.54 (1H, d, J=7.3Hz), 6.65-6.75 (2H, m), 6.85 (1H, d, J=2.5Hz), 6.95-7.33 (13H, m)

MASS (+ APCI) : 420 ($M^+ + 1$)

5

(4) 1-[(3,4-Dihydro-5-hydroxy-2-naphthyl)methyl]-3-diphenylmethyl-2(1H)-pyridone

mp : 196-197°C

IR (Nujol) : 3250, 1640 cm^{-1}

10

NMR ($\text{DMSO}-d_6$, δ) : 2.10 (2H, t, J=8.3Hz), 2.64 (2H, t, J=8.3Hz), 4.63 (2H, s), 5.65 (1H, s), 5.96 (1H, s), 6.24 (1H, t, J=6.8Hz), 6.42 (1H, d, J=7.2Hz), 6.64 (1H, d, J=7.5Hz), 6.85-7.35 (12H, m), 7.55-7.60 (1H, m), 9.24 (1H, s)

15

MASS (+ APCI) : 420 ($M^+ + 1$)

Preparation 21

A mixture of (1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl N,N-diphenylcarbamate (100 mg) and N-chlorosuccinimide (35.8 mg) in 1,4-dioxane (1.5 ml) was stirred at 100°C for 5 hours, cooled to room temperature, and partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford (6- or 8-chloro-1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl N,N-diphenylcarbamate (62 mg) as colorless solids.

25

mp : 138-144°C

30

IR (Nujol) : 3320, 1675, 1575, 1220 cm^{-1}

NMR (CDCl_3 , δ) : 1.20-1.41 (1H, m), 1.85-2.1 (2H, m), 2.18-2.32 (1H, m), 2.42-2.56 (1H, m), 2.74-2.94 (2H, m), 4.07-4.28 (2H, m), 4.91 (1H, s), 6.54 (1H, d, J=8.5Hz), 7.05 (1H, d, J=8.5Hz), 7.16-7.39 (10H, m)

35

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(+) APCI MS m/z : 408 ($M^+ + 1$)Preparation 22

5 A solution of diethyl azodicarboxylate (871 mg) in tetrahydrofuran (4 ml) was added slowly to a stirred solution of (1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methanol (961 mg), phthalimide (736 mg), and triphenylphosphine (1.31 g) in tetrahydrofuran (10 ml) at room temperature and the resulting mixture was stirred at 10 the same temperature for 24 hours. The reaction mixture was evaporated in vacuo and the residue was chromatographed (toluene) over silica gel. The eluate was evaporated in vacuo and the residue was triturated with 15 n-hexane to afford N-[(1,2,3,4-tetrahydro-5-methoxy-2-naphthyl)methyl]phthalimide (888 mg) as a colorless powder.

mp : 143-144°C

IR (Nujol) : 1770, 1705, 1580, 1260 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.33-1.55 (1H, m), 1.93-2.03 (1H, m), 2.15-2.25 (1H, m), 2.35-2.63 (2H, m), 2.75-2.97 (2H, m), 3.71 (2H, d, $J=7.1\text{Hz}$), 3.79 (3H, s), 6.62-6.69 (2H, m), 7.06 (1H, t, $J=7.9\text{Hz}$), 7.68-7.77 (2H, m), 7.82-7.90 (2H, m)

(+) APCI MS m/z : 322 ($M^+ + 1$)

25

Preparation 23

The following compound was obtained according to a similar manner to that of Preparation 4.

30 N-[(1,2,3,4-Tetrahydro-5-hydroxy-2-naphthyl)methyl]-phthalimide

IR (Nujol) : 3310, 1765, 1690, 1585 cm^{-1}

35 NMR ($\text{DMSO}-d_6$, δ) : 1.38 (1H, m), 1.91 (1H, m), 2.05 (1H, m), 2.34-2.5 (2H, m), 2.69-2.77 (2H, m), 3.58 (2H, d, $J=7.0\text{Hz}$), 6.47 (1H, d, $J=7.4\text{Hz}$),

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6.56 (1H, d, J=7.4Hz), 6.86 (1H, t, J=7.4Hz),
7.81-7.93 (4H, m), 9.15 (1H, s)
(+) APCI MS m/z : 308 (M⁺+1)

5 Preparation 24

A solution of N-[(1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl]phthalimide (634 mg) and hydrazine monohydrate (309 mg) in ethanol (14 ml) was refluxed for 3 hours, cooled to room temperature, and evaporated in vacuo. The residue was chromatographed (methylene chloride - methanol) over basic alumina to afford 6-(aminomethyl)-5,6,7,8-tetrahydro-1-naphthol (281 mg) as a colorless powder.

mp : 183-192°C

15 IR (Nujol) : 3350-3100, 2750-2300, 1580 cm⁻¹
NMR (DMSO-d₆, δ) : 1.11-1.32 (1H, m), 1.58 (1H, m),
1.91-1.97 (1H, m), 2.23-2.45 (2H, m), 2.68-2.80
(2H, m), 3.1 (3H, br), 6.49 (1H, d, J=7.6Hz),
6.55 (1H, d, J=7.8Hz), 6.85 (1H, t, J=7.7Hz)
20 (+) APCI MS m/z : 178 (M⁺+1)

Preparation 25

A solution of 4-nitrophenyl chloroformate (2.02 g) in dichloromethane (15 ml) was added dropwise to a stirred solution of benzhydrol (1.84 g) and pyridine (1.19 g) in dichloromethane (18 ml) under ice cooling. The resulting mixture was stirred at the same temperature for a while and allowed to stand at room temperature for 3 days. The reaction mixture was washed successively with ice-water, ice-1N hydrochloric acid, and ice-brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford benzhydryl (4-nitrophenyl)carbonate (3.32 g) as colorless crystals.

35 mp : 53-59°C

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IR (Film) : 1770, 1520, 1345, 1260-1180 cm^{-1} NMR (CDCl_3 , δ) : 6.81 (1H, s), 7.30-7.47 (12H, m),
8.25 (2H, d, $J=9.2\text{Hz}$)(+) APCI-MS m/z : 167

5

Preparation 26

A solution of 6-aminomethyl)-5,6,7,8-tetrahydro-1-naphthol (23 mg) and 4-nitrophenyl(benzhydryl)carbonate (45 mg) in N,N -dimethylformamide (0.5 ml) was stirred at 50°C for 2 hours, cooled to room temperature, and extracted with ethyl acetate. The extract was washed successively with water, sodium bicarbonate aqueous solution (three times) and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford benzhydryl N-[(1,2,3,4-tetrahydro-5-hydroxy-2-naphthyl)methyl]carbamate (40 mg) as an oil.

10

15

IR (Film) : 3350, 1695 cm^{-1} NMR (CDCl_3 , δ) : 1.35-1.45 (1H, m), 1.94 (2H, m),
2.45-2.6 (2H, m), 2.76-2.86 (2H, m), 3.22 (2H, t, $J=6.3\text{Hz}$), 5.04 (1H, m), 6.58 (1H, d, $J=7.9\text{Hz}$), 6.64 (1H, d, $J=7.6\text{Hz}$), 6.81 (1H, s), 6.97 (1H, t, $J=7.8\text{Hz}$), 7.15-7.35 (11H, m)

20

(+) APCI MS m/z : 167

25

Preparation 27

(6RS)-5,6,7,8-Tetrahydro-6-[(1S)-1-phenylethyl)-amino]-1-naphthol was prepared from (2RS)-1,2,3,4-tetrahydro-5-methoxy-N-[(1S)-1-phenylethyl)-2-naphthylamine hydrochloride in a similar manner to that of Preparation 9.

30

IR (Film) : 3500-3350, 1585 cm^{-1} NMR (CDCl_3 , δ) : 1.38 (3H, d, $J=6.6\text{Hz}$), 1.5-2.2 (3H, m), 2.45-2.65 (2H, m), 2.75-2.85 (2H, m), 4.05 (1H, q, $J=6.6\text{Hz}$), 6.4-7.35 (9H, m)

35

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(+) APCI MS m/z : 268 ($M^+ + 1$)Preparation 28

5 A solution of (6RS)-5,6,7,8-tetrahydro-6-[(1S)-1-phenylethyl]amino]-1-naphthol (267 mg) in dimethylsulfoxide (3 ml) was added dropwise to a stirred suspension of 60% sodium hydride (44 mg, washed with n-hexane) in dimethylsulfoxide (0.5 ml) at room temperature in a nitrogen atmosphere over 15 minutes, and
10 the mixture was stirred at 50°C for 10 minutes and cooled to room temperature. Ethyl bromoacetate (167 mg) in dimethylsulfoxide (1 ml) was added thereto and the resulting mixture was stirred at the same temperature for 2 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed
15 twice with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (dichloromethane-ethanol) over silica gel to afford ethyl [(6RS)-5,6,7,8-tetrahydro-6-[(1S)-1-phenylethyl]amino]-1-naphthyloxy]acetate (243 mg) as a brown oil.
20

IR (Film) : 3320, 1755, 1730 (shoulder), 1585, 1195 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=7.1\text{Hz}$), 1.37 (3H, d, $J=6.6\text{Hz}$), 1.48 (3H, br m), 2.09 (1H, br m),
25 2.48-3.02 (4H, m), 4.04 (1H, q, $J=6.6\text{Hz}$), 4.25 (2H, q, $J=7.1\text{Hz}$), 4.58 (2H, s), 6.49 (1H, d, $J=8.0\text{Hz}$), 6.67 (1H, d, $J=8.0\text{Hz}$), 7.01 (1H, t, $J=8.0\text{Hz}$), 7.20-7.33 (5H, m)

(+) APCI MS : 354 ($M^+ + 1$)

30

Preparation 29

Ethyl [(6RS)-5,6,7,8-tetrahydro-6-[(1S)-1-phenylethyl]amino]-1-naphthyloxy]acetate (185 mg) was converted to the hydrochloride using 4N hydrogen chloride
35 in ethyl acetate in a usual manner. A mixture of the

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hydrochloride, 10% palladium on carbon (50% wet, 100 mg), and ammonium formate (330 mg) in ethanol (40 ml) was stirred under reflux for 30 minutes and the hot reaction mixture was filtered. The filtrate was evaporated in vacuo and the residue was partitioned between ethyl acetate and sodium bicarbonate aqueous solution. The ethyl acetate layer was dried over sodium sulfate and evaporated in vacuo to ethyl [(6RS)-6-amino-5,6,7,8-tetrahydro-1-naphthyloxy]acetate (95 mg) as an oil.

IR (Film) : 3600-3150, 1750, 1730 (shoulder), 1580, 1195 cm^{-1}

NMR (CDCl_3 , δ) : 1.30 (3H, t, $J=7.1\text{Hz}$), 1.46-1.66 (3H, m), 2.01 (1H, m), 2.48-2.78 (2H, m), 2.92-3.16 (3H, m), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.62 (2H, s), 6.53 (1H, d, $J=8.0\text{Hz}$), 6.74 (1H, d, $J=7.6\text{Hz}$), 7.05 (1H, t, $J=7.8\text{Hz}$)

Preparation 30

A suspension of (5-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)methanol (0.20 g), ethyl bromoacetate (0.15 ml), potassium iodide (catalytic amount) and potassium carbonate (0.20 g) in acetonitrile (10 ml) was stirred under reflux for 2.5 hours. The solvent was removed and the residue was partitioned between ether and 1N hydrochloric acid. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane - ethyl acetate) over silica gel to afford (5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthyl)methanol (0.29 g) as an oil.

IR (Film) : 3400, 1730 cm^{-1}

NMR (CDCl_3 , δ) : 1.44 (1H, t, $J=5.4\text{Hz}$), 1.80-1.95 (4H, m), 2.63-2.98 (3H, m), 3.80 (2H, dd, $J=5.4, 5.4\text{Hz}$), 4.26 (2H, q, $J=7.1\text{Hz}$), 4.62 (2H, s), 6.56 (1H, d, $J=7.9\text{Hz}$), 6.89 (1H, d, $J=7.9\text{Hz}$),

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7.09 (1H, dd, $J=7.9, 7.9\text{Hz}$)MASS (APCI) m/z : 265 (M^++1), 247 ($M^++1 - H_2O$)Preparation 31

- 5 To a solution of diethylcarbonate (10.3 ml) and sodium hydride (4.2 g, 60% in oil) in toluene (300 ml) was added 5-t-butyldiphenylsilyloxy-1-oxo-1,2,3,4-tetrahydronaphthalene (17 g) at 100°C. The mixture was stirred for 4 hours at the same temperature and then the cooled solution was washed with sat. NaHCO_3 and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give 5-t-butyldiphenylsilyloxy-2-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene (20 g).
- 10
- 15 IR (neat) : 1730, 1680 cm^{-1}
NMR (CDCl_3 , δ) : 1.11 (9H, s), 1.25 (3H, t, $J=7\text{Hz}$), 2.3-2.7 (2H, m), 2.8-3.4 (2H, m), 3.60 (1H, dd, $J=5.2, 10.4\text{Hz}$), 4.28 (2H, q, $J=7\text{Hz}$), 6.4-6.8 (2H, m), 7.2-7.8 (11H, m)
- 20 MS m/z : 473 (M^++1)

Preparation 32

- To a solution of 5-t-butyldiphenylsilyloxy-2-ethoxycarbonyl-1-oxo-1,2,3,4-tetrahydronaphthalene (17 g) in a mixture of ethanol (100 ml) and tetrahydrofuran (100 ml) was added NaBH_4 (1.4 g) at 0°C. After the mixture was stirred for 6 hours at room temperature, the solvent was removed in vacuo. The residue was dissolved in a mixture of ethyl acetate and water and the organic solution was washed with 1N-HCl solution, sat. NaHCO_3 , and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give 1-hydroxy-2-ethoxycarbonyl-5-t-butyldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (7.9 g).
- 25
- 30
- 35 IR (neat) : 3450, 1730 cm^{-1}

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NMR (CDCl₃, δ) : 1.10 (9H, s), 1.26 (3H, t, J=7Hz),
2.2-2.5 (2H, m), 2.5-3.4 (4H, m), 4.16 (2H, q,
J=7Hz), 5.02 (1H, m), 6.2-6.4 (1H, m), 6.7-7.0
(2H, m), 7.2-7.8 (10H, m)

5

Preparation 33

To a solution of 1-hydroxy-2-ethoxycarbonyl-5-t-
butyldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (5.9
g) in toluene (100 ml) was added KHSO₄ (2.0 g). The
10 mixture was stirred for 1 hour under reflux, and then the
cooled solution was washed with sat. NaHCO₃ and brine.
The dried solvent was evaporated in vacuo and the residue
was purified by chromatography on silica gel to give 2-
ethoxycarbonyl-5-t-butyldiphenylsilyloxy-3,4-
15 dihydronaphthalene (7.4 g).

IR (neat) : 1700 cm⁻¹

NMR (CDCl₃, δ) : 1.11 (9H, s), 1.35 (3H, t, J=7Hz),
2.5-2.7 (2H, m), 3.03 (2H, t, J=8.8Hz), 4.27
(2H, q, J=7Hz), 6.3-6.5 (1H, m), 6.7-6.8 (2H,
20 m), 7.1-7.8 (11H, m)

MS m/z : 457 (M⁺+1)

Preparation 34

A solution of AD-mix-α (trade name, Aldrich) (9.2 g)
25 in a mixture of t-butyl alcohol (30 ml) and water (30 ml)
was stirred for 1 hour and then methanesulfonamide (0.62
g) and 2-ethoxycarbonyl-5-t-butyldiphenylsilyloxy-3,4-
dihydronaphthalene (3.0 g) were added to the solution at
room temperature. After being stirred for 20 hours at the
30 same temperature, sodium sulfite (9.0 g) was added, and
the mixture was stirred for 30 minutes. The mixture was
partitioned between ethyl acetate and water. The organic
layer was washed with 1N-HCl solution, sat. NaHCO₃, and
brine, dried over MgSO₄, and evaporated in vacuo. The
35 residue was purified by chromatography on silica gel to

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afford (1S,2R)-1,2-dihydroxy-2-ethoxycarbonyl-5-t-butylidiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (3.1 g).

IR (neat) : 3450, 1705 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.09 (9H, s), 1.25 (3H, t, $J=7.0\text{Hz}$), 2.1-2.3 (2H, m), 2.50 (1H, d, $J=10.8\text{Hz}$), 2.9-3.2 (2H, m), 3.58 (1H, s), 4.35 (2H, q, $J=7.0\text{Hz}$), 5.03 (1H, d, $J=10.8\text{Hz}$), 6.32 (1H, d, $J=8.0\text{Hz}$), 6.80 (1H, t, $J=8.0\text{Hz}$), 7.14 (1H, d, $J=8.0\text{Hz}$), 7.3-7.8 (10H, m)

10 MS m/z : 470 (M^+-17)

HPLC : chiralcel AD, 5% isopropanol/hexane, 12.9 ml/min

15 Preparation 35

The following compound was obtained by using AD-mix- β (trade name, Aldrich) instead of AD-mix- α in a similar manner to that of Preparation 34.

20 (1R,2S)-1,2-Dihydroxy-2-ethoxycarbonyl-5-t-butylidiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene

HPLC : chiralcel AD, 5% isopropanol/hexane, 11.0 ml/min

25 Preparation 36

To a solution of 2-methoxycarbonyl-5-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (3.9 g) in tetrahydrofuran (50 ml) were added NaH (0.73 g, 60% in oil) and then methyl iodide (3 ml) at 0°C under N_2 . After being stirred for 1 hour at room temperature, the solution was poured into a mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 2-methyl-2-methoxycarbonyl-5-methoxy-1-oxo-1,2,3,4-

30

35

- 70 -

tetrahydronaphthalene (4.0 g).

IR (Neat) : 1720, 1680 cm^{-1}

NMR (CDCl_3 , δ) : 1.49 (3H, s), 1.9-2.1 (1H, m),
2.4-3.0 (3H, m), 3.66 (3H, m), 3.88 (3H, m),
5 7.01 (1H, d, $J=8\text{Hz}$), 7.26 (1H, t, $J=8\text{Hz}$), 7.68
(1H, d, $J=8\text{Hz}$)

MS m/z : 249 (M^++1)

Preparation 37

10 To a solution of 2-methyl-2-methoxycarbonyl-5-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene (2.0 g) in trifluoroacetic acid (20 ml) was added triethylsilane (2.0 ml) at room temperature. After being stirred for 6 hours at room temperature, the solution was poured into a
15 mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 2-methyl-2-methoxycarbonyl-5-methoxy-1,2,3,4-
20 tetrahydronaphthalene (4.0 g).

IR (neat) : 1720 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (3H, s), 1.6-2.3 (2H, m), 2.5-
2.8 (3H, m), 3.20 (1H, d, $J=16\text{Hz}$), 3.66 (3H, m),
3.80 (3H, m), 6.64 (1H, d, $J=8\text{Hz}$), 6.70 (1H, d,
25 $J=8\text{Hz}$), 7.08 (1H, t, $J=8\text{Hz}$)

MS m/z : 235 (M^++1)

Preparation 38

30 To a solution of diethylphosphoric acid ethyl ester (19 g) in dimethoxyethane (200 ml) was added NaH (3.4 g, 60% in oil) at 0°C under N_2 . After being stirred for 30 minutes, 5-*t*-butyldiphenylsilyloxy-1-oxo-1,2,3,4-tetrahydronaphthalene (20 g) was added to the mixture. After being stirred for 12 hours at 80°C , the solution was
35 poured into a mixture of ethyl acetate and water. The

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organic layer was washed with 1N-HCl solution, sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was dissolved into a mixture of toluene (100 ml) and 1,8-diazabicyclo[5.4.0]-7-undecene (17 ml) and the mixture was stirred for 3 days at 100°C. The solution was washed with 1N-HCl solution, sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 5-t-butylldiphenylsilyloxy-1-ethoxycarbonylmethyl-3,4-dihydronaphthalene (20.3 g).

IR (neat) : 1740 cm⁻¹

NMR (CDCl₃, δ) : 1.10 (9H, m), 1.25 (3H, t, J=7Hz), 2.2-2.4 (2H, m), 2.99 (2H, t, J=8.2Hz), 3.40 (2H, s), 4.17 (2H, q, J=7Hz), 6.00 (1H, m), 6.3-

6.5 (1H, m), 6.6-6.8 (2H, m), 7.3-7.8 (10H, m)

MS m/z : 471 (M⁺+1)

Preparation 39

To a solution of diisopropylamine (17 ml) in THF (tetrahydrofuran) (210 ml) was added n-butyllithium (67 ml, 1.6N in hexane) at -78°C under N₂. The solution was stirred for 30 minutes at 0°C and then cooled to -78°C. To the solution was added ethyl acetate (12 g) and the mixture was stirred for 30 minutes at the same temperature to give Li-enolate solution. A solution of 5-t-butylldiphenylsilyloxy-1-oxo-1,2,3,4-tetrahydronaphthalene (10 g) in THF (50 ml) was cooled to -78°C, the above Li-enolate solution (35 ml) was added, and stirred for 1 hour at the same temperature. The mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 1-hydroxy-1-ethoxycarbonylmethyl-5-t-butylldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (8.0 g).

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IR (neat) : 3400, 1705 cm^{-1}

NMR (CDCl_3 , δ) : 1.10 (9H, s), 1.27 (3H, t, $J=7\text{Hz}$),
1.6-2.2 (4H, m), 2.7-3.0 (4H, m), 4.20 (2H, q,
 $J=7\text{Hz}$), 6.30 (1H, d, $J=8\text{Hz}$), 6.77 (1H, t,
 $J=8\text{Hz}$), 7.10 (1H, d, $J=8\text{Hz}$), 7.2-7.8 (10H, m)

MS m/z : 471 (M^+-17)Preparation 40

(1) To a solution of (1S,2R)-1,2-dihydroxy-2-ethoxycarbonyl-5-t-butyl-diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (1.8 g) in CH_2Cl_2 (20 ml) were added triphenylphosphine (2.9 g) and CBr_4 (4.9 g) at the room temperature. After being stirred for 1 hour, ethyl acetate (200 ml) was added to the solution. After filtration, mother liquid was washed with water, sat. NaHCO_3 , and brine. The dried solvent was evaporated in vacuo to give a residue.

(2) The residue obtained above was purified by chromatography on silica gel. The obtained oil was dissolved into tetrahydrofuran (30 ml) and LiAlH_4 (420 mg) was added at 0°C . The mixture was stirred for 2 hours at the same temperature, quenched with 1N-HCl, and partitioned between ethyl acetate and water. The organic layer was washed with water, sat. NaHCO_3 , and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel to give (2R)-2-hydroxy-2-hydroxymethyl-5-t-butyl-diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (1.8 g).

IR (neat) : 3500, 1600 cm^{-1}

NMR (CDCl_3 , δ) : 1.10 (9H, s), 1.8-2.0 (4H, m), 2.85 (2H, s), 3.00 (2H, t, $J=7.0\text{Hz}$), 3.59 (2H, m), 6.29 (1H, d, $J=8.0\text{Hz}$), 6.6-6.8 (2H, m), 7.3-7.8 (10H, m)

MS m/z : 397 (M^+-35)

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Preparation 41

The following compound was obtained according to a similar manner to that of Preparation 40.

5 (2S)-2-Hydroxy-2-hydroxymethyl-5-t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene

Preparation 42

10 The following compound was obtained according to a similar manner to that of Preparation 1.

5-t-Butyldiphenylsilyloxy-1-(2-hydroxyethyl)-3,4-dihydronaphthalene

IR (neat) : 3400-3300 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.06 (9H, s), 2.2-2.4 (2H, m),
2.6-3.0 (4H, m), 3.76 (2H, t, $J=6.4\text{Hz}$), 5.96
(1H, m), 6.36 (1H, d, $J=8\text{Hz}$), 6.7-6.9 (2H, m),
7.2-7.8 (10H, m)

MS m/z : 429 (M^++1)

20

Preparation 43

To a solution of 5-t-butyldiphenylsilyloxy-2-hydroxymethyl-3,4-dihydronaphthalene (1.0 g) in benzene (10 ml) were added diethylzinc (7.2 ml, 1M solution in
25 hexane) and diiodomethane (1.2 ml) at 0°C under N_2 . After being stirred for 4 hours at room temperature, the solution was poured into a mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated
30 in vacuo. The residue was purified by chromatography on silica gel to afford 5-t-butyldiphenylsilyloxy-1,2-methylene-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene.

Preparation 44

35 The following compound was obtained according to a

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similar manner to that of Preparation 43.

1,2-Methylene-1-(2-hydroxyethyl)-5-t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene

5 IR (neat) : 3400-3300, 1700 cm^{-1}

NMR (CDCl_3 , δ) : 0.7-0.9 (2H, m), 1.08 (9H, s),
1.2-1.5 (2H, m), 1.7-2.5 (3H, m), 2.6-2.9 (1H,
m), 3.1-3.3 (1H, m), 3.7-3.9 (2H, m), 6.27 (1H,
d, $J=8\text{Hz}$), 6.72 (1H, t, $J=8\text{Hz}$), 6.99 (1H, d,
10 $J=8\text{Hz}$), 7.2-7.8 (10H, m)

MS m/z : 443 (M^++1)

Preparation 45

To a solution of 5-t-butyl-
15 diphenylsilyloxy-1-(2-hydroxyethyl)-3,4-dihydronaphthalene (1.0 g) in CH_2Cl_2 (30 ml) were added Na_2CO_3 (290 mg) and m-chloroperbenzoic acid (750 mg) at 0°C . After being stirred for 2 hours, the solvent was removed in vacuo. The residue was extracted with ethyl acetate. The mixture was washed with 1N-HCl
20 solution, sat. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was dissolved into tetrahydrofuran (20 ml) and LiAlH_4 (200 mg) was added at 0°C . After being stirred for 2 hours, the reaction was quenched by saturated potassium sodium tartrate solution.
25 After filtration, the solvent was removed, and the residue was purified by chromatography on silica gel to afford (cis)-5-t-butyl-
diphenylsilyloxy-1-(2-hydroxyethyl)-2-
hydroxy-1,2,3,4-tetrahydronaphthalene (1.1 g).

IR (neat) : 3300 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.10 (9H, s), 1.8-2.3 (4H, m),
2.8-3.2 (3H, m), 3.6-4.2 (3H, m), 6.2-6.4 (1H,
m), 6.6-6.8 (2H, m), 7.0-7.8 (10H, m)

MS m/z : 429 (M^+-17)

35

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Preparation 46

A mixture of (2R)-2-hydroxy-2-hydroxymethyl-5-t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (1.4
g) and N,N-diphenylcarbamoyl chloride (3 g) in pyridine
5 (15 ml) was stirred at 100°C for 12 hours, cooled to room
temperature, and partitioned between ethyl acetate and 1N-
HCl. The organic layer was washed with water, sat.
NaHCO₃, and brine. The dried solvent was evaporated in
vacuo and the residue was purified by chromatography on
10 silica gel to give (2R)-2-hydroxy-2-(N,N-
diphenylcarbamoyloxymethyl)-5-t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (1.3 g).

IR (neat) : 3400, 1700 cm⁻¹

15 NMR (CDCl₃, δ) : 1.10 (9H, s), 1.8-2.0 (3H, m),
2.6-3.1 (4H, m), 4.16 (2H, s), 6.25 (1H, d,
J=8.0Hz), 6.53 (1H, d, J=8Hz), 6.68 (1H, t,
J=8Hz), 7.2-7.8 (20H, m)

MS m/z : 628 (M⁺+1)

20 HPLC : chiralcel OD, 10% isopropanol/hexane,
12.0 ml/min

Preparation 47

The following compounds were obtained according to a
similar manner to that of Preparation 46.

25

(1) (2S)-2-Hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-
t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene

HPLC : chiralcel OD, 10% isopropanol/hexane,
10.1 ml/min

30

(2) (cis)-1-Hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-
t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene

35 NMR (CDCl₃, δ) : 1.08 (9H, s), 1.6-2.1 (3H, m),
2.5-3.2 (2H, m), 4.0-4.2 (1H, m), 4.4-4.8 (2H,
m), 6.32 (1H, d, J=8Hz), 6.6-6.9 (2H, m),

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7.1-7.8 (20H, m)

MS m/z : 610 ($M^+ - 1$)

- 5 (3) (trans)-1-Hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-
5-t-butylidiphenylsilyloxy-1,2,3,4-
tetrahydronaphthalene
NMR ($CDCl_3$, δ) : 1.08 (9H, s), 1.4-2.1 (3H, m),
2.6-3.1 (2H, m), 4.13 (1H, dd, $J=11.2$, 5.2Hz),
4.48 (1H, d, $J=8$ Hz), 4.62 (1H, dd, $J=11.2$,
10 4.4Hz), 6.30 (1H, d, $J=8$ Hz), 6.77 (1H, t,
 $J=8$ Hz), 7.08 (1H, c, $J=8$ Hz), 7.1-7.8 (20H, m)
MS m/z : 610 ($M^+ - 1$)
- 15 (4) 5-t-Butyldiphenylsilyloxy-1,2-methylene-2-(N,N-
diphenylcarbamoyloxymethyl)-1,2,3,4-
tetrahydronaphthalene
IR (neat) : 1700 cm^{-1}
NMR ($CDCl_3$, δ) : 0.8-1.2 (2H, m), 1.6-1.9 (2H, m),
2.0-2.3 (1H, m), 3.1-3.4 (1H, m), 4.20 (1H, d,
20 $J=11.2$ Hz), 4.30 (1H, d, $J=11.2$ Hz), 6.25 (1H, d,
 $J=8$ Hz), 6.6-7.0 (2H, m), 7.1-7.8 (20H, m)
- 25 (5) 5-t-Butyldiphenylsilyloxy-1,2-methylene-1-[2-(N,N-
diphenylcarbamoyloxy)ethyl]-1,2,3,4-
tetrahydronaphthalene
IR (neat) : 1700 cm^{-1}
NMR ($CDCl_3$, δ) : 0.6-0.9 (2H, m), 1.08 (9H, s),
1.2-2.5 (5H, m), 2.6-3.1 (2H, m), 4.0-4.4 (2H,
30 m), 6.24 (1H, d, $J=8$ Hz), 6.65 (1H, t, $J=8$ Hz),
6.96 (1H, d, $J=8$ Hz), 7.1-7.8 (20H, m)
- 35 (6) 1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-5-t-
butyldiphenylsilyloxy-3,4-dihydronaphthalene
IR (neat) : 1705 cm^{-1}
NMR ($CDCl_3$, δ) : 1.10 (9H, s), 2.1-2.3 (2H, m),

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2.72 (2H, t, J=6.6Hz), 2.90 (2H, t, J=8.0Hz),
4.30 (2H, t, J=7.0Hz), 5.78 (1H, t, J=4.4Hz),
6.33 (1H d, J=8Hz), 6.6-6.9 (2H, m), 7.1-7.8
(20H, m)

5 MS m/z : 624 ($M^+ + 1$)

(7) (cis)-5-t-Butyldiphenylsilyloxy-1-[2-(N,N-
diphenylcarbamoyloxy)ethyl]-2-hydroxy-1,2,3,4-
tetrahydronaphthalene

10 IR (neat) : 1700 cm^{-1}

NMR (CDCl_3 , δ) : 1.10 (9H, s), 1.6-2.3 (4H, m),
2.7-3.2 (3H, m), 4.0-4.4 (3H, m), 6.25 (1H, d,
J=8Hz), 6.49 (1H, d, J=8Hz), 6.66 (1H, t,
J=8Hz), 7.1-7.8 (20H, m)

15

Preparation 48

2-(N,N-Diphenylcarbamoyloxymethyl)-5-t-
butyldiphenylsilyloxy-3,4-dihydronaphthalene was prepared
from 2-ethoxycarbonyl-5-t-butyldiphenylsilyloxy-3,4-
20 dihydronaphthalene in similar manners to those of
Preparations 13 and 46.

IR (neat) : 1710 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.10 (9H, m), 2.23 (2H, t,
J=8.4Hz), 2.97 (2H, t, J=8.4Hz), 4.77 (2H, s),
6.23 (1H, s), 6.31 (1H, d, J=8Hz), 6.50 (1H, d,
J=6.8Hz), 6.68 (1H, t, J=8Hz), 7.2-7.8 (20H, m)

Preparation 49

2-(N,N-Diphenylcarbamoyloxymethyl)-2-methyl-5-
30 methoxy-1,2,3,4-tetrahydronaphthalene was prepared from
2-methoxycarbonyl-2-methyl-5-methoxy-1,2,3,4-
tetrahydronaphthalene in similar manners to those of
Preparations 1 and 46.

IR (neat) : 1700 cm^{-1}

35 NMR (CDCl_3 , δ) : 0.83 (3H, s), 1.4 (2H, m),

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2.2-2.8 (4H, m), 3.80 (3H, m), 3.90 (1H, d, J=10.4Hz), 4.00 (1H, d, J=10.4Hz), 6.59 (1H, d, J=8Hz), 6.63 (1H, d, J=8Hz), 7.08 (1H, t, J=8Hz), 7.1-7.5 (10H, m)

5 MS m/z : 402 (M^+ +1)

Preparation 50

1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-1-hydroxy-5-t-butyl-
10 butyldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene was prepared from 1-ethoxycarbonylmethyl-1-hydroxy-5-t-butyl-
diphenylsilyloxy-1,2,3,4-tetrahydronaphthalene in similar
manners to those of Preparations 1 and 46.

IR (neat) : 3450, 1710 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.09 (9H, s), 1.6-2.2 (6H, m),
2.7-3.0 (2H, m), 4.33 (2H, t, J=6.6Hz), 6.26
(1H, d, J=8Hz), 6.78 (1H, t, J=8Hz), 6.96 (1H,
d, J=8Hz), 7.1-7.8 (20H, m)

MS m/z : 626 (M^+ -17)

20 Preparation 51

5-t-Butyldiphenylsilyloxy-1,2-dihydroxy-1-[2-(N,N-
diphenylcarbamoyloxy)ethyl]-1,2,3,4-tetrahydronaphthalene
was prepared from 5-t-butyldiphenylsilyloxy-1-[2-(N,N-
diphenylcarbamoyloxy)ethyl]-3,4-dihydronaphthalene in a
25 similar manner to that of Example 21.

IR (neat) : 3500-3400, 1700 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.09 (9H, m), 1.7-2.2 (4H, m),
2.6-3.1 (2H, m), 3.8-4.0 (1H, m), 4.1-4.4 (2H,
m), 6.32 (1H, d, J=8Hz), 6.77 (1H, t, J=8Hz),
7.01 (1H, d, J=8Hz), 7.1-7.8 (20H, m)

Preparation 52

A solution of 5-t-butyldiphenylsilyloxy-1,2-
dihydroxy-1-[2-(N,N-diphenylcarbamoyloxy)ethyl]-1,2,3,4-
35 tetrahydronaphthalene (2.0 g) and p-toluenesulfonic acid

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(20 mg) in toluene (40 ml) was stirred for 30 minutes under reflux. The mixture was washed with 1N-HCl solution, sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 5-t-butyl-diphenylsilyloxy-1-[2-(N,N-diphenylcarbamoyloxy)ethyl]-2-oxo-1,2,3,4-tetrahydronaphthalene (1.0 g).

IR (neat) : 1800, 1705 cm⁻¹

NMR (CDCl₃, δ) : 1.12 (9H, s), 2.0-2.6 (4H, m), 2.7-3.0 (1H, m), 3.1-3.4 (2H, m), 4.0-4.2 (2H, m), 6.40 (1H, d, J=8Hz), 6.48 (1H, d, J=8Hz), 6.76 (1H, t, J=8Hz), 7.1-7.8 (20H, m)

MS m/z : 638 (M⁺+1)

15 Preparation 53

To a solution of 5-t-butyl-diphenylsilyloxy-1-[2-(N,N-diphenylcarbamoyloxy)ethyl]-2-oxo-1,2,3,4-tetrahydronaphthalene (0.9 g) in THF (tetrahydrofuran) (20 ml) was added methylmagnesium bromide (2.0 ml, 1M solution in THF) at 0°C under N₂. After being stirred for 1 hour at the room temperature, the solution was poured into a mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution, sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 5-t-butyl-diphenylsilyloxy-1-[2-(N,N-diphenylcarbamoyloxy)ethyl]-2-hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalene (0.6 g).

IR (neat) : 3400, 1705 cm⁻¹

NMR (CDCl₃, δ) : 1.11 (9H, s), 1.22 (3H, s), 1.6-2.6 (5H, m), 2.6-3.2 (2H, m), 4.0-4.4 (2H, m), 6.27 (1H, d, J=8Hz), 6.39 (1H, d, J=8Hz), 6.65 (1H, t, J=8Hz), 7.1-7.8 (20H, m)

MS m/z : 638 (M⁺-18)

35 Preparation 54

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To a solution of 1-[2-(N,N-diphenylcarbamoyloxy)-ethyl]-5-t-butylidiphenylsilyloxy-3,4-dihydronaphthalene (2.0 g) in THF (tetrahydrofuran) (20 ml) was added BH₃ (4.8 ml, 1M solution in THF) at 0°C under N₂. After being
5 stirred for 12 hours at the room temperature, 2N-NaOH solution (1.5 ml) and H₂O₂ (1.0 ml, 35% solution) were added to the solution and stirred for 4 hours. The mixture was poured into a mixture of ethyl acetate and water. The organic layer was washed with 1N-HCl solution,
10 sat. NaHCO₃, and brine, dried over MgSO₄, and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford (trans)-1-[2-(N,N-diphenylcarbamoyloxy)ethyl]-2-hydroxy-5-t-butylidiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene (1.1 g).

15 IR (neat) : 3400, 1700 cm⁻¹
NMR (CDCl₃, δ) : 1.10 (9H, s), 1.7-2.1 (4H, m),
2.7-3.0 (3H, m), 3.9-4.0 (1H, m), 4.1-4.3 (2H, m), 6.24 (1H, d, J=8Hz), 6.49 (1H, d, J=8Hz),
6.67 (1H, t, J=8Hz), 7.1-7.8 (20H, m)

20 MS m/z : 642 (M⁺+1)

Preparation 55

A solution of methyl [5-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthyl]formate (2.50 g), D-10-
25 camphorsulfonic acid (124 mg), [RuCl₂(S)-binap]₂NEt₃ (90 mg) [cf. Tetrahedron Letters, Vol. 35, No. 26, pp 4559-4562, 1994], ethyl acetate (23.8 ml) and methanol (1.25 ml) was stirred under hydrogen (90 atm) at 50°C for 40 hours. The reaction mixture was evaporated in vacuo and
30 the residue was purified by silica gel column chromatography (n-hexane:ethyl acetate = 4:1) to give (1R,2S)-methyl [1-hydroxy-5-methoxy-1,2,3,4-tetrahydro-2-naphthyl]formate (2.47 g) as a white powder.

mp : 87-88°C

35

Example 9

The following compounds were obtained according to a similar manner to that of Example 7.

- 5 (1) (S)-2-[(1,2,3,4-Tetrahydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
[α]_D²⁶ = -20.63° (C=0.95, CH₂Cl₂)
IR (Film) : 1750, 1660, 1580, 760, 720, 700 cm⁻¹
NMR (CDCl₃, δ) : 1.35-1.60 (1H, m), 1.29 (3H, t,
10 J=7.1Hz), 1.80-2.00 (1H, m), 2.20-3.20 (5H, m),
4.15-4.20 (2H, m), 4.25 (2H, q, J=7.1Hz), 4.61
(2H, s), 5.45 (1H, s), 6.51 (1H, d, J=7.8Hz),
6.64 (1H, d, J=7.8Hz), 6.86 (1H, d, J=9.5Hz),
7.08 (1H, dd, J=7.8Hz, 7.8Hz), 7.10-7.35 (11H,
15 m)
- (2) 2-[(3,4-Dihydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
IR (Film) : 1740, 1660, 1600 cm⁻¹
NMR (CDCl₃, δ) : 1.30 (3H, t, J=7.1Hz), 2.23 (2H, t,
20 J=8.3Hz), 2.86 (2H, t, J=8.3Hz), 4.26 (2H, q,
J=7.1Hz), 4.62 (2H, s), 4.84 (2H, s), 5.44 (1H,
s), 6.26 (1H, s), 6.50-6.70 (2H, m), 6.85-6.90
(1H, m), 7.00-7.35 (12H, m)
25 MASS (+ APCI) : 507 (M⁺+1)
- (3) 1-[(3,4-Dihydro-5-ethoxycarbonylmethoxy)-2-naphthyl)methyl]-5-diphenylmethyl-2(1H)-pyridone
IR (Film) : 1750, 1660, 1600 cm⁻¹
NMR (CDCl₃, δ) : 1.30 (3H, t, J=7.1Hz), 2.17 (2H, t,
30 J=8.1Hz), 2.85 (2H, t, J=8.1Hz), 4.27 (2H, q,
J=7.1Hz), 4.62 (2H, s), 5.23 (1H, s), 6.14 (1H,
s), 6.50-6.70 (3H, m), 6.80-6.85 (1H, m), 7.05-
7.35 (12H, m)
35 MASS (+ APCI) : 506 (M⁺+1)

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- (4) 1-[(3,4-Dihydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-3-diphenylmethyl-2(1H)-pyridone
IR (Film) : 1750, 1660, 1600 cm^{-1}
NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7.1\text{Hz}$), 2.20 (2H, t, $J=8.6\text{Hz}$), 2.89 (2H, t, $J=8.6\text{Hz}$), 4.25 (2H, q, $J=7.1\text{Hz}$), 4.61 (2H, s), 4.71 (2H, s), 5.30 (1H, s), 5.82 (1H, s), 6.12 (1H, t, $J=6.8\text{Hz}$), 6.60-6.70 (3H, m), 7.00-7.35 (12H, m)
MASS (+ APCI) : 506 (M^++1)

Example 10

The following compounds were obtained according to a similar manner to that of Example 1.

- (1) [1,2,3,4-Tetrahydro-5-(methoxycarbonylmethoxy)-2-naphthyl]methyl N,N-diphenylcarbamate
mp : 89.5-91°C
IR (Nujol) : 1765, 1710, 1590, 1205 cm^{-1}
NMR (CDCl_3 , δ) : 1.23-1.44 (1H, m), 1.86-2.01 (2H, m), 2.35-2.75 (3H, m), 2.90-2.99 (1H, m), 3.79 (3H, s), 4.07-4.23 (2H, m), 4.62 (2H, s), 6.51 (1H, d, $J=8.0\text{Hz}$), 6.69 (1H, d, $J=7.6\text{Hz}$), 7.03 (1H, t, $J=7.8\text{Hz}$), 7.16-7.38 (10H, m)
(+) APCI MS m/z : 446 (M^++1)
- (2) [6-or 8-Chloro-1,2,3,4-tetrahydro-5-(methoxycarbonylmethoxy)-2-naphthyl]methyl N,N-diphenylcarbamate
IR (Film) : 1755, 1705 cm^{-1}
NMR (CDCl_3 , δ) : 1.25-1.36 (1H, m), 1.8-2.05 (2H, m), 2.18-2.33 (1H, m), 2.4-2.65 (1H, m), 2.82-3.02 (2H, m), 3.79 (3H, s), 4.07-4.27 (2H, m), 4.61 (2H, s), 6.48 (1H, d, $J=8.7\text{Hz}$), 7.12 (1H, d, $J=8.7\text{Hz}$), 7.16-7.39 (10H, m)
(+) APCI MS m/z : 480 (M^++1)

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(3) Benzhydryl N-[(1,2,3,4-tetrahydro-5-(methoxycarbonylmethoxy)-2-naphthyl)methyl]carbamate
mp : 101-102°C

IR (Nujol) : 3350, 3320, 1765, 1680, 1250, 1215 cm⁻¹

5 NMR (CDCl₃, δ) : 1.35-1.43 (1H, m), 1.94 (2H, m),
2.36-2.59 (2H, m), 2.78-3.03 (2H, m), 3.22 (2H,
t, J=6.4Hz), 3.79 (3H, s), 4.63 (2H, s), 4.99
(1H, m), 6.51 (1H, d, J=8.0Hz), 6.71 (1H, d,
J=7.6Hz), 6.81 (1H, s), 7.03 (1H, t, J=7.9Hz),
10 7.15-7.35 (10H, m)
(+) APCI MS m/z : 167

Example 11

To a solution of (2R)-2-hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-t-butyldiphenylsilyloxy-
15 1,2,3,4-tetrahydronaphthalene (1.9 g) in THF
(tetrahydrofuran) (20 ml) was added tetrabutylammonium
fluoride (5 ml, 1N-THF solution). After being stirred for
1 hour at the room temperature, the solution was extracted
20 with ethyl acetate. The mixture was washed with water and
brine. The dried solvent was evaporated in vacuo. The
obtained oil was dissolved into N,N-dimethylformamide (10
ml) and then K₂CO₃ (1.0 g) and ethyl bromoacetate (0.6 ml)
were added at room temperature. The mixture was stirred
25 for 2 hours at the same temperature and partitioned
between ethyl acetate and water. The organic layer was
washed with water, sat. NaHCO₃, and brine. The dried
solvent was evaporated in vacuo and the residue was
purified by chromatography on silica gel to give (2R)-2-
30 hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-
ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene (1.1
g).

IR (neat) : 3400, 1720, 1700 cm⁻¹

35 NMR (CDCl₃, δ) : 1.25 (3H, t, J=7Hz), 1.6-2.0 (2H,
m), 2.6-3.0 (4H, m), 4.10 (2H, s), 4.14 (2H, q,

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J=7Hz), 4.60 (2H, s), 6.52 (1H, d, J=8Hz), 6.66 (1H, d, J=8Hz), 7.10 (1H, t, J=8Hz), 7.2-7.5 (10H, m)

MS m/z : 476 ($M^+ + 1$)

5 HPLC : chiralcel AD, 50% ethanol/hexane,
12.8 ml/min

Example 12

10 The following compounds were obtained according to a similar manner to that of Example 11.

(1) (2S)-2-Hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphthalene

15 HPLC : chiralcel AD, 50% ethanol/hexane,
11.7 ml/min

(2) 2-(N,N-Diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethoxy-3,4-dihydronaphthalene

IR (neat) : 1740, 1705 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.29 (3H, t, J=7Hz), 2.18 (2H, t, J=8.4Hz), 2.87 (2H, t, J=8.4Hz), 4.25 (2H, q, J=7Hz), 4.61 (2H, s), 4.75 (2H, s), 6.25 (1H, s), 6.5-6.7 (2H, m), 7.06 (1H, t, J=8Hz), 7.2-7.5 (10H, m)

25

(3) (cis)-2-(N,N-Diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3400, 1740, 1700 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.25 (3H, t, J=7Hz), 1.4-2.1 (3H, m), 2.4-3.2 (3H, m), 4.25 (2H, q, J=7Hz), 4.4-4.7 (5H, m), 6.63 (1H, d, J=8Hz), 6.99 (1H, d, J=8Hz), 7.15 (1H, t, J=8Hz), 7.2-7.5 (10H, m);

MS m/z : 458 ($M^+ - 17$)

35

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- (4) (trans)-2-(N,N-Diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3400, 1740, 1695 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.27 (3H, t, $J=7\text{Hz}$), 1.4-2.1 (3H, m), 2.5-3.1 (2H, m), 4.16 (1H, m), 4.25 (2H, q, $J=7\text{Hz}$), 4.47 (1H, d, $J=8.4\text{Hz}$), 4.61 (2H, s), 4.63 (1H, m), 6.59 (1H, d, $J=8\text{Hz}$), 7.1-7.5 (12H, m)

10 MS m/z : 458 (M^+-17)

- (5) 1,2-Methylene-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 1700, 1740 cm^{-1}

15 NMR (CDCl_3 , δ) : 0.8-1.1 (2H, m), 1.25 (3H, t, $J=7\text{Hz}$), 1.5-2.2 (3H, m), 3.1-3.3 (1H, m), 4.1-4.4 (4H, m), 4.69 (2H, s), 6.54 (1H, d, $J=8\text{Hz}$), 6.85 (1H, d, $J=8\text{Hz}$), 7.05 (1H, t, $J=8\text{Hz}$), 7.1-7.5 (10H, m)

20

- (6) 1,2-Methylene-1-[2-N,N-diphenylcarbamoyloxy)ethyl]-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 1700, 1740 cm^{-1}

25 NMR (CDCl_3 , δ) : 1.6-1.9 (2H, m), 1.25 (3H, t, $J=8\text{Hz}$), 1.2-2.2 (5H, m), 2.6-3.1 (2H, m), 4.0-4.4 (4H, m), 4.60 (2H, s), 6.50 (1H, d, $J=8\text{Hz}$), 7.0-7.5 (12H, m)

MS m/z : 486 (M^++1)

- 30 (7) 1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-2-hydroxy-2-methyl-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3400, 1740, 1690 cm^{-1}

35 NMR (CDCl_3 , δ) : 1.23 (3H, s), 1.4-2.0 (4H, m), 2.2-2.8 (3H, m), 2.9-3.1 (1H, m), 4.0-4.4 (4H,

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m), 4.59 (2H, m), 6.52 (2H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.1-7.4 (10H, m)

MS m/z : 486 ($M^+ - 17$)

- 5 (8) (cis)-1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-2-hydroxy-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3400, 1730, 1680 cm^{-1}

10 NMR (CDCl_3 , δ) : 1.25 (3H, t, J=7Hz), 1.6-2.3 (5H, m), 2.6-3.0 (3H, m), 4.0-4.5 (5H, m), 4.61 (2H, s), 6.52 (1H, d, J=8Hz), 6.61 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 7.1-7.4 (10H, m)

MS m/z : 490 ($M^+ + 1$)

- 15 (9) (trans)-1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-2-hydroxy-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3400, 1700-1720 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.25 (3H, t, J=7Hz), 1.7-2.0 (4H, m), 2.6-3.0 (3H, m), 3.8-4.0 (1H, m), 4.1-4.4 (4H, m), 4.60 (2H, s), 6.52 (1H, d, J=8Hz), 6.61 (1H, d, J=8Hz), 7.04 (1H, t, J=8Hz), 7.1-7.4 (10H, m)

MS m/z : 490 ($M^+ + 1$)

25

- (10) 1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-1-hydroxy-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

IR (neat) : 3450, 1720, 1705 cm^{-1}

30 NMR (CDCl_3 , δ) : 1.25 (3H, t, J=7Hz), 1.6-2.2 (6H, m), 2.8-3.0 (2H, m), 3.7-3.9 (2H, m), 4.1-4.4 (2H, m), 4.60 (2H, s), 6.5-6.9 (2H, m), 6.96 (1H, d, J=8Hz), 7.1-7.4 (10H, m)

MS m/z : 472 ($M^+ - 17$)

- 35 (11) 1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-5-

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ethoxycarbonylmethyloxy-3,4-dihydronaphthalene

IR (neat) : 1740, 1705 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=7\text{Hz}$), 2.1 (2H, m),
2.7-2.9 (4H, m), 4.2-4.4 (4H, m), 4.61 (2H, s),
5.79 (1H, t, $J=4.4\text{Hz}$), 6.59 (1H, d, $J=8\text{Hz}$), 6.94
(1H, d, $J=8\text{Hz}$), 7.01 (1H, t, $J=8\text{Hz}$), 7.1-7.4
(10H, m)

Example 13

To a methylene chloride solution (10 ml) of 2-[2-(5-methoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.25 g) was added a methylene chloride solution of boron tribromide (1N, 0.78 ml) at -5°C , and the solution was stirred at the same temperature for 4 hours. The reaction mixture was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was crude 2-[2-(5-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.34 g).

A N,N-dimethylformamide solution (15 ml) of crude 2-[2-(5-hydroxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.34 g), potassium carbonate (0.16 g) and ethyl bromoacetate (0.2 ml) was stirred at room temperature for 24 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane - ethyl acetate = 3:2) over silica gel to afford 2-[2-(5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.17 g) as a pale yellow oil.

IR (CH_2Cl_2 solution) : 1750, 1660, 1585 cm^{-1}

NMR (CDCl_3 , δ) : 1.50-2.02 (6H, m), 2.04-2.58 (1H, m), 2.80-2.95 (2H, m), 4.10-4.31 (4H, m), 4.60 (2H, s), 5.45 (1H, s), 6.50 (1H, d, $J=7.9\text{Hz}$),

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6.72 (1H, d, J=7.9Hz), 6.84 (1H, d, J=9.5Hz),
6.97-7.54 (12H, m)

MASS (APCI) m/z : 523 (M⁺+1)

5 Example 14

The following compound was obtained according to a similar manner to that of Example 13.

2-(N,N-Diphenylcarbamoyloxymethyl)-2-methyl-5-
10 ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene
IR (neat) : 1740, 1700 cm⁻¹
NMR (CDCl₃, δ) : 0.83 (3H, s), 1.25 (3H, t, J=7Hz),
1.52 (2H, m), 2.2-2.9 (4H, m), 3.92 (1H, d,
J=10.2Hz), 4.00 (1H, d, J=10.2Hz), 4.24 (2H, q,
15 J=7Hz), 4.60 (2H, s), 6.50 (1H, d, J=8Hz), 6.64
(1H, d, J=8Hz), 7.06 (1H, t, J=8Hz), 7.2-7.5
(10H, m)
MS m/z : 474 (M⁺+1)

20 Example 15

To a solution of 2-(N,N-Diphenylcarbamoyloxymethyl)-
5-t-butyldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene
(1.3 g) in CH₂Cl₂ (30 ml) were added Na₂CO₃ (290 mg) and
m-chloroperbenzoic acid (550 mg) at 0°C. After being
25 stirred for 2 hours, the solvent was removed in vacuo.

The residue was extracted with ethyl acetate. The
mixture was washed with 1N-HCl solution, sat. NaHCO₃, and
brine, dried over MgSO₄, and evaporated in vacuo. The
residue was purified by chromatography on silica gel to
30 afford 1,2-epoxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-t-
butyldiphenylsilyloxy-1,2,3,4-tetrahydronaphthalene. This
compound was treated in a similar manner to that of
Example 11 to give 1,2-epoxy-2-(N,N-
diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-
35 1,2,3,4-tetrahydronaphthalene (370 mg).

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IR (neat) : 1720 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=7\text{Hz}$), 1.6-1.9 (1H, m), 2.1-2.5 (2H, m), 3.0-3.2 (1H, m), 3.59 (1H, m), 4.23 (2H, q, $J=7\text{Hz}$), 4.58 (2H, s), 6.73 (1H, d, $J=8\text{Hz}$), 6.93 (1H, d, $J=8\text{Hz}$), 7.08 (1H, t, $J=8\text{Hz}$), 7.1-7.7 (10H, m)

MS m/z : 474 (M^++1)Example 16

10 To a solution of 5-*t*-butyldiphenylsilyloxy-1-[2-(*N,N*-diphenylcarbamoyloxy)ethyl]-2-hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalene (800 mg) in toluene (20 ml) was added KHSO_4 (100 mg). The mixture was stirred for 1 hour under reflux, and then the cooled solution was washed with
15 sat. NaHCO_3 and brine. The dried solvent was evaporated in vacuo and the residue was dissolved in THF (tetrahydrofuran) (20 ml). To the solution was added tetrabutylammonium fluoride (2 ml, 1N-THF solution). After being stirred for 1 hour at the room temperature,
20 the solution was extracted with ethyl acetate. The mixture was washed with water and brine. The dried solvent was evaporated in vacuo. The obtained oil was dissolved into *N,N*-dimethylformamide (5 ml) and ethyl bromoacetate (0.2 ml) was added thereto at room
25 temperature. The mixture was stirred for 2 hours at the same temperature and partitioned between ethyl acetate and water. The organic layer was washed with water, sat. NaHCO_3 , and brine. The dried solvent was evaporated in vacuo and the residue was purified by chromatography on
30 silica gel to give 1-[2-(*N,N*-diphenylcarbamoyloxy)ethyl]-2-methyl-5-ethoxycarbonylmethyloxy-3,4-dihydronaphthalene (310 mg).

IR (neat) : 1740, 1700 cm^{-1}

35 NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=8\text{Hz}$), 1.89 (3H, s), 1.9-2.2 (1H, m), 2.8-3.3 (3H, m), 3.42 (1H, m),

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3.8-4.1 (1H, m), 4.1-4.4 (4H, m), 4.62 (2H, s),
6.54 (1H, d, J=8Hz), 6.62 (1H, d, J=8Hz), 7.07
(1H, t, J=8Hz), 7.1-7.5 (10H, m)

MS m/z : 486 ($M^+ + 1$)

5

Example 17

A mixture of ethyl [5,6,7,8-tetrahydro-6-(2-hydroxyethyl)-1-naphthyloxy]acetate (50 mg),
N,N-diphenylcarbamoyl chloride (50 mg), and pyridine (32
10 mg) was stirred at 100°C for 1 hour and 40 minutes, cooled
to room temperature, and partitioned between ethyl acetate
and 1N hydrochloric acid. The ethyl acetate layer was
washed successively with water, aqueous sodium
bicarbonate, and brine, dried over magnesium sulfate, and
15 evaporated in vacuo. The residue was chromatographed
(toluene - ethyl acetate) over silica gel to afford 2-[5-(ethoxycarbonylmethoxy)-1,2,3,4-tetrahydro-2-naphthyl]-
ethyl N,N-diphenylcarbamate (31 mg) as a syrup.

IR (Film) : 1755, 1705, 1195 cm^{-1}

20 NMR (CDCl_3 , δ) : 1.30 (3H, t, J=7.1Hz), 1.25-1.42
(1H, m), 1.61-1.70 (3H, m), 1.86-1.93 (1H, m),
2.29-2.64 (2H, m), 2.71-2.97 (2H, m), 4.20-4.32
(4H, m), 4.61 (2H, s), 6.51 (1H, d, J=8.0Hz),
6.67 (1H, d, J=7.6Hz), 7.03 (1H, t, J=7.9Hz),
25 7.13-7.36 (10H, m)

(+) APCI MS m/z : 474 ($M^+ + 1$), 261

Example 18

To a methylene chloride solution (1 ml) of phosgene
30 dimer (0.027 ml) was added a methylene chloride solution
(2 ml) of (5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthyl)methanol (0.12 g) and pyridine (0.1 ml) at -5°C,
and the solution was stirred at room temperature for two
hours. To the reaction mixture was added a solution of
35 1,1-diphenylhydrazine hydrochloride (0.10 g) and pyridine

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(0.05 ml) in methylene chloride (2 ml). The solution was stirred at room temperature for 3 hours, washed with 5% hydrochloric acid, water, and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane - ethyl acetate) over silica gel to afford 2-[(5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthyl)methoxycarbonyl]-1,1-diphenylhydrazine (0.13 g) as colorless solids.

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7.1Hz), 1.65-2.00 (3H, m), 2.44-3.32 (4H, m), 4.25 (2H, q, J=7.1Hz), 4.15-4.44 (2H m), 4.62 (2H, s), 6.56 (1H, d, J=7.8Hz), 6.65-7.20 (8H, m), 7.20-7.40 (5H, m)

MASS (APCI) m/z : 475 (M⁺+1)

Example 19

A solution of ethyl (6-amino-5,6,7,8-tetrahydro-1-naphthyloxy)acetate (83 mg) and 4-nitrophenyl(benzhydryl)-carbonate (116 mg) in N,N-dimethylformamide (2 ml) was stirred at 50°C for 1 hour and 30 minutes, cooled to room temperature, and extracted with ethyl acetate. The extract was washed five times with aqueous sodium bicarbonate and with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford benzhydryl N-[1,2,3,4-tetrahydro-5-(ethoxycarbonylmethoxy)-2-naphthyl]carbamate (110 mg) as an oil.

IR (Film) : 1750, 1720, 1705, 1210 cm⁻¹

NMR (CDCl₃, δ) : 1.29 (3H, t, J=7.1Hz), 1.79 (1H, m), 2.04 (1H, m), 2.65 (1H, dd, J=16.4, 8.0Hz), 2.79-2.89 (2H, m), 3.11 (1H, dd, J=16.3, 4.5Hz), 4.04 (1H, m), 4.26 (2H, q, J=7.1Hz), 4.62 (2H, s), 4.91 (1H, br d), 6.54 (1H, d, J=8.1Hz), 6.71 (1H, d, J=7.6Hz), 6.81 (1H, s), 7.06 (1H, t,

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J=7.9Hz), 7.15-7.35 (10H, m)

(+) APCI MS m/z : 167

Example 20

- 5 60% Sodium hydride (10.2 mg) was added to a stirred
solution of benzhydryl N-[[1,2,3,4-tetrahydro-5-
(methoxycarbonylmethoxy)-2-naphthyl)methyl]carbamate (117
mg) and methyl iodide (36 mg) in N,N-dimethylformamide
(1.2 ml) under ice cooling and the mixture was stirred at
10 the same temperature for 7 hours, then another 60% sodium
hydride (10.2 mg) and methyl iodide (36 mg) was added
thereto. The resulting mixture was stirred at room
temperature for 3 days and extracted with ethyl acetate.
The extract was washed twice with brine, dried over
15 magnesium sulfate, and evaporated in vacuo. The residue
was chromatographed (toluene - ethyl acetate) over silica
gel to afford benzhydryl N-methyl-N-[[1,2,3,4-tetrahydro-
5-(methoxycarbonylmethoxy)-2-naphthyl)methyl]carbamate (71
mg) as an oil.
- 20 IR (Film) : 1755, 1730 (shoulder), 1690, 1200 cm^{-1}
NMR (CDCl_3 , δ) : 1.25-1.45 (1H, m), 1.85-2.15 (2H,
m), 2.35-2.8 (3H, m), 2.96 and 3.08 (3H, s),
3.05 (1H, m), 3.3-3.5 (2H), 3.79 (3H, s), 4.63
(2H), 6.51 (1H, d, J=7.9Hz), 6.66 (1H, m), 6.82
25 (1H, s), 7.03 (1H, m), 7.18-7.33 (10H, m)
(+) APCI MS m/z : 167

Example 21

- 30 To a solution of 2-(N,N-diphenylcarbamoyloxymethyl)-
5-ethoxycarbonylmethyloxy-3,4-dihydronaphthalene (270 mg)
in a mixture of acetonitrile (10 ml) and water (5 ml) were
added 4-methylmorpholine N-oxide (0.34 ml) and OsO_4 (1 ml,
2.5% in t-butyl alcohol) at 0°C. After being stirred for
4 hours, the solution was diluted into ethyl acetate. The
35 mixture was washed with 1N-HCl solution, sat. NaHCO_3 , and

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brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 1,2-dihydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene.

5 IR (neat) : 3400, 1720 cm^{-1}
NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7\text{Hz}$), 1.6-2.2 (2H, m), 2.6-3.2 (4H, m), 4.25 (2H, q, $J=7\text{Hz}$),
4.4-4.6 (3H, m), 4.61 (2H, s), 6.61 (1H, m),
7.1-7.6 (12H, m)
10 MS m/z : 474 (M^+-17)

Example 22

The following compound was obtained according to a similar manner to that of Example 21.

15 1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-1,2-dihydroxy-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene
IR (neat) : 3450, 1740, 1705 cm^{-1}
NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=7\text{Hz}$), 1.7-2.2 (4H, m), 2.6-3.0 (2H, m), 3.82 (1H, m), 4.2-4.4 (4H, m), 4.59 (2H, s), 6.50 (1H, m), 7.1-7.4 (12H, m)
20 MS m/z : 488 (M^+-17)

Example 23

25 To a solution of 1,2-epoxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene (0.2 g) in CH_2Cl_2 (30 ml) was added HF-pyridine (0.5 ml) at 0°C . After being stirred for 2 hours, the solvent was removed in vacuo.
30 The residue was extracted with ethyl acetate. The mixture was washed with 1N-HCl solution, sat. NaHCO_3 , and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 1-fluoro-2-hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene
35

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(70 mg).

IR (neat) : 1700 cm^{-1}

NMR (CDCl_3 , δ) : 1.26 (3H, t, $J=7\text{Hz}$), 1.5-2.1 (4H, m), 2.6-3.0 (2H, m), 4.0-4.5 (4H, m), 4.62 (2H, m), 5.20 (1H, d, $J=52\text{Hz}$), 6.69 (1H, m), 7.0-7.5 (12H, m)

MS m/z : 494 (M^++1)Example 24

To a solution of 2-hydroxy-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene (100 mg) in CH_2Cl_2 (10 ml) was added diethylaminosulfur trifluoride (0.5 ml) at -78°C . After being stirred for 30 minutes, the mixture was washed with sat. NaHCO_3 and brine, dried over MgSO_4 , and evaporated in vacuo. The residue was purified by chromatography on silica gel to afford 2-fluoro-2-(N,N-diphenylcarbamoyloxymethyl)-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene (40 mg).

NMR (CDCl_3 , δ) : 1.25 (3H, d, $J=7\text{Hz}$), 1.6-2.0 (2H, m), 2.8-3.0 (4H, m), 4.26 (2H, q, $J=7\text{Hz}$), 4.27 (2H, d, $J=22\text{Hz}$), 4.76 (2H, s), 6.54 (1H, d, $J=8\text{Hz}$), 6.64 (1H, d, $J=8\text{Hz}$), 7.06 (1H, t, $J=8\text{Hz}$), 7.1-7.5 (10H, m)

MS m/z : 478 (M^++1)Example 25

The following compound was obtained according to a similar manner to that of Example 24.

1-[2-(N,N-Diphenylcarbamoyloxy)ethyl]-2-fluoro-5-ethoxycarbonylmethyloxy-1,2,3,4-tetrahydronaphthalene

NMR (CDCl_3 , δ) : 1.25 (3H, t, $J=7\text{Hz}$), 1.7-2.1 (4H, m), 2.6-2.9 (2H, m), 4.1-4.4 (4H, m), 4.60 (2H, s), 6.5-6.7 (2H, m), 7.0-7.4 (11H, m)

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MS m/z : 492 ($M^+ + 1$)Example 26

A solution of 2-[(3,4-dihydro-5-ethoxycarbonylmethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.20 g) and 3-chloroperoxybenzoic acid (94 mg) in dichloromethane (5 ml) was allowed to stand in a freezer (about -15°C) for overnight. The reaction mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and sodium hydrogencarbonate solution. The organic layer was separated and washed with water, brine, dried over magnesium sulfate and evaporated in vacuo. The residue and 10% palladium on carbon in ethyl acetate (5 ml) and acetic acid (one drop) were stirred under hydrogen (1 atm) at room temperature for 4 hours. The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (n-hexane-ethyl acetate = 2:1-1:1) to give 2-[(1,2,3,4-tetrahydro-5-ethoxycarbonylmethoxy-2-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone (0.08 g) as a pale yellow oil.

IR (CH_2Cl_2) : 3600-3100, 1750, 1660 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, $J=7.1\text{Hz}$), 1.60-2.00 (2H, m), 2.75-3.00 (4H, m), 4.20-4.35 (4H, m), 4.61 (2H, s), 5.43 (1H, s), 6.53 (1H, d, $J=8\text{Hz}$), 6.61 (1H, d, $J=8\text{Hz}$), 6.90-7.35 (13H, m)

MASS (+ APCI) : 525 ($M^+ + 1$)Example 27

A solution of 2-[(5-ethoxycarbonylmethoxy-1,2,3,4-tetrahydro-1-naphthyl)methoxycarbonyl]-1,1-diphenylhydrazine (0.17 g) and 1N-aqueous sodium hydroxide (1 ml) in dioxane (1.5 ml) was stirred at room temperature for 30 minutes and partitioned between 5% hydrochloric

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acid and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was washed with isopropanol to afford 2-[(5-carboxymethoxy-1,2,3,4-tetrahydro-1-naphthyl)-methoxycarbonyl]-1,1-diphenylhydrazine (0.08 g) as a colorless powder.

IR (Nujol) : 3230, 1730, 1700 cm^{-1}

NMR (CD_3OD , δ) : 1.49-2.01 (4H, m), 2.70-3.13 (3H, m), 4.10-4.47 (2H, m), 4.48 (2H, s), 6.62-7.30 (14H, m)

MASS (APCI) m/z : 447 ($M^+ + 1$)

Example 28

The following compounds were obtained according to similar manners to those of Examples 3, 4 and 8.

(1) (S)-2-[(1,2,3,4-Tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
[α] $_D^{25}$ = -27.6° (C=0.75, CH_2Cl_2)
mp : 144-145°C
IR (Nujol) : 2600-2200, 1740, 1640, 770, 700 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ) : 1.20-1.45 (1H, m), 1.70-1.90 (1H, m), 2.10-2.90 (5H, m), 3.90-4.10 (2H, m), 4.65 (2H, s), 5.57 (1H, s), 6.55-6.65 (2H, m), 6.90-7.05 (2H, m), 7.20-7.35 (11H, m), 12.96 (1H, br s)

MASS (+ APCI) : 481 ($M^+ + 1$)

(2) 2-[(3,4-Dihydro-5-carboxymethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
mp : 156-158°C
IR (Nujol) : 1710, 1630 cm^{-1}
NMR ($\text{DMSO}-d_6$, δ) : 2.12 (2H, t, $J=8.9\text{Hz}$), 2.67 (2H, t, $J=8.9\text{Hz}$), 4.66 (2H, s), 4.74 (2H, s), 5.56 (1H, s), 6.13 (1H, s), 6.62 (1H, d, $J=7.9\text{Hz}$),

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6.71 (1H, d, J=7.9Hz), 6.95 (1H, d, J=9.6Hz),
7.05 (1H, d, J=7.9Hz), 7.15-7.40 (11H, m), 13.0
(1H, br s)

MASS (+ APCI) : 479 ($M^+ + 1$)

5

(3) 2-[(1,2,3,4-Tetrahydro-5-carboxymethoxy-2-hydroxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone
mp : 122-123°C

IR (Nujol) : 3600-3200, 1730, 1650 cm^{-1}

10

NMR (CDCl_3 , δ) : 1.50-1.90 (2H, m), 2.50-3.00 (4H, m), 3.82 (2H, br s), 4.23 (1H, d, J=13.9Hz), 4.37 (1H, d, J=13.9Hz), 4.63 (2H, s), 5.44 (1H, s), 6.50-6.65 (2H, m), 6.95-7.40 (13H, m)

MASS (+ APCI) : 497 ($M^+ + 1$)

15

(4) 1-[(3,4-Dihydro-5-carboxymethoxy-2-naphthyl)methyl]-5-diphenylmethyl-2(1H)-pyridone

mp : 181-182°C

IR (Nujol) : 1730, 1650 cm^{-1}

20

NMR ($\text{DMSO}-d_6$, δ) : 2.11 (2H, t, J=8.3Hz), 2.72 (2H, t, J=8.3Hz), 4.61 (2H, s), 4.69 (2H, s), 5.41 (1H, s), 6.03 (1H, s), 6.43 (1H, d, J=10.2Hz), 6.60 (1H, d, J=7.4Hz), 6.72 (1H, d, J=8.0Hz), 7.00-7.35 (13H, m), 12.98 (1H, br s)

25

MASS (+ APCI) : 478 ($M^+ + 1$)

(5) 1-[(3,4-Dihydro-5-carboxymethoxy-2-naphthyl)methyl]-3-diphenylmethyl-2(1H)-pyridone

mp : 186-188°C

30

IR (Nujol) : 1750, 1640 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.13 (2H, t, J=8.2Hz), 2.74 (2H, t, J=8.2Hz), 4.66 (2H, s), 5.65 (1H, s), 5.99 (1H, s), 6.25 (1H, t, J=6.8Hz), 6.59 (1H, d, J=7.3Hz), 6.71 (1H, d, J=8.0Hz), 6.87 (1H, d, J=6.7Hz), 7.00-7.35 (11H, m), 7.59 (1H, d,

35

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J=6.7Hz)

(6) 2-[2-(5-Carboxymethoxy-1,2,3,4-tetrahydro-1-naphthyl)ethyl]-6-diphenylmethyl-3(2H)-pyridazinone

5 NMR (CD₃OD, δ) : 1.60-2.25 (6H, m), 2.55-2.90 (3H, m), 4.11-4.29 (2H, m), 4.47 (2H, s), 5.55 (1H, s), 6.54-6.61 (2H, m), 6.88-6.90 (2H, m), 7.17-7.35 (11H, m)

10 MASS (APCI) m/z : 495 (M⁺+1)

(7) 2-[5-(Carboxymethoxy)-1,2,3,4-tetrahydro-2-naphthyl]ethyl N,N-diphenylcarbamate

mp : 175-177.5°C

IR (Nujol) : 2750-2250, 1765, 1675 cm⁻¹

15 NMR (DMSO-d₆, δ) : 1.24 (1H, m), 1.57 (3H, m), 1.79 (1H, m), 2.2-2.5 (2H, m), 2.65-2.85 (2H, m), 4.19 (2H, m), 4.65 (2H, s), 6.56-6.64 (2H, m), 7.00 (1H, t, J=7.8Hz), 7.18-7.39 (10H, m)

(+) APCI MS m/z : 446 (M⁺+1), 233

20 (8) [5-(Carboxymethoxy)-2-methyl-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate

IR (Nujol) : 1700 cm⁻¹

25 NMR (CDCl₃, δ) : 0.83 (3H, s), 1.44 (2H, m), 2.2-2.9 (4H, m), 3.92 (1H, d, J=10.6Hz), 4.08 (1H, d, J=10.6Hz), 4.65 (2H, s), 6.53 (1H, d, J=8Hz), 6.66 (1H, d, J=8Hz), 7.06 (1H, t, J=8Hz), 7.2-7.5 (10H, m)

30 FAB MS m/z : 446 (M⁺+1)

Example 29

A solution of benzhydryl N-[[1,2,3,4-tetrahydro-5-(methoxycarbonylmethoxy)-2-naphthyl]methyl]carbamate (60 mg) in a mixture of 1N sodium hydroxide aqueous solution
35 (0.20 ml), methanol (1 ml), and 1,2-dimethoxyethane (1 ml)

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was stirred at room temperature for 30 minutes,
neutralized with 1N hydrochloric acid, and extracted with
ethyl acetate. The extract was washed with brine, dried
over magnesium sulfate, and evaporated in vacuo. The oily
5 residue was powdered from diisopropyl ether to afford
benzhydryl N-[[1,2,3,4-tetrahydro-5-(carboxymethoxy)-2-
naphthyl]methyl]carbamate (51 mg) as a colorless powder.

mp : 160-161°C

IR (Nujol) : 3350, 2800-2300, 1755, 1685 cm⁻¹

10 NMR (DMSO-d₆, δ) : 1.2-1.35 (1H, m), 1.84 (2H, m),
2.25-2.5 (2H, m), 2.7-2.85 (2H, m), 3.01 (2H,
m), 4.64 (2H, s), 6.56-6.67 (3H, m), 7.00 (1H,
t, J=7.8Hz), 7.30-7.38 (10H, m), 7.57 (1H, t),
12.9 (1H, br)

15 (+) APCI MS m/z : 412

Example 30

The following compound was obtained according to a
similar manner to that of Example 29.

20

[6- or 8-Chloro-5-(carboxymethoxy)-1,2,3,4-
tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate

mp : 138-144.5°C

IR (Nujol) : 2700-2300, 1740, 1710 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.23 (1H, br m), 1.84 (2H, br m),
2.12-2.27 (1H, m), 2.35-2.6 (1H, m), 2.7-2.85
(2H, m), 4.05-4.15 (2H, m), 4.66 (2H, s), 6.69
(1H, d, J=8.8Hz), 7.15-7.42 (11H, m)

(+) APCI MS m/z : 466 (M⁺+1)

30

Example 31

To a solution of (2R)-2-hydroxy-2-(N,N-diphenyl-
carbamoyloxymethyl)-5-ethoxycarbonylmethoxy-1,2,3,4-
tetrahydronaphthalene (0.9 g) in ethanol (20 ml) was added
35 1N-NaOH solution (1.9 ml). After being stirred for 4

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hours at the same temperature, the solvent was removed in vacuo to give sodium salt of (2R)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (0.9 g).

- 5 IR (Nujol) : 3400, 1700, 1580 cm^{-1}
 NMR (D_2O , δ) : 1.2-1.6 (2H, m), 2.1-2.6 (4H, m),
 3.72 (1H, d, $J=11.0\text{Hz}$), 3.85 (1H, d, $J=11.0\text{Hz}$),
 4.13 (2H, s), 6.29 (2H, m), 6.4-7.0 (11H, m)
- 10 FAB MS m/z : 470 (M^++1)
 HPLC : chiralcel AGP, 8% acetonitrile/0.02N
 phosphate buffer (pH=6.0), 5.3 ml/min

Example 32

- 15 The following compounds were obtained according to similar manners to those of Examples 6 and 31.

- (1) Sodium salt of benzhydryl N-[5-(carboxymethoxy)-1,2,3,4-tetrahydro-2-naphthyl]carbamate
- 20 mp : 209-223°C (dec.)
 IR (Nujol) : 3340, 1695, 1615, 1250 cm^{-1}
 NMR ($\text{DMSO}-d_6$, δ) : 1.57 (1H, m), 1.94 (1H, m),
 2.51-2.67 (2H, m), 2.83-2.92 (2H, m), 3.60 (1H, m),
 4.10 (2H, s), 6.48-6.56 (2H, m), 6.69 (1H, s),
25 6.94 (1H, t, $J=7.9\text{Hz}$), 7.26-7.38 (10H, m),
 7.57 (1H, d, $J=7.2\text{Hz}$)
 FAB MS m/z : 454 (M^++1), 432
- (2) Sodium salt of (2S)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
- 30 HPLC : chiralcel AGP, 8% acetonitrile/0.02N
 phosphate buffer (pH=6.0), 7.4 ml/min
- 35 (3) Sodium salt of [5-(carboxymethoxy)-3,4-dihydro-2-

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naphthyl)methyl N,N-diphenylcarbamate

IR (Nujol) : 1710 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.0-2.2 (2H, m), 2.6-2.8 (2H, m),
4.08 (2H, s), 4.68 (2H, s), 6.21 (1H, s), 6.50
(1H, d, J=8Hz), 6.60 (1H, d, J=8Hz), 6.98 (1H,
t, J=8Hz), 7.2-7.5 (10H, m)

FAB MS m/z : 452 (M^+ +1)

(4) Sodium salt of [5-(carboxymethoxy)-1,2-dihydroxy-
1,2,3,4-tetrahydro-2-naphthyl)methyl N,N-
diphenylcarbamate

IR (Nujol) : 3400, 1650-1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.6-1.8 (2H, m), 2.5-2.8 (2H, m),
4.0-4.9 (5H, s), 6.53 (1H, m), 6.9-7.5 (12H, m)

FAB MS m/z : 486 (M^+ +1)

(5) Sodium salt of [5-(carboxymethoxy)-1,2-epoxy-1,2,3,4-
tetrahydro-2-naphthyl)methyl N,N-diphenylcarbamate

IR (Nujol) : 1700, 1590 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.4-1.7 (1H, m), 1.9-2.2 (2H, m),
2.8-3.1 (1H, m), 3.65 (1H, s), 4.08 (2H, s),
4.20 (1H, d, J=12.0Hz), 4.52 (1H, d, J=12.0Hz),
6.71 (1H, d, J=8Hz), 6.84 (1H, d, J=8Hz), 7.05
(1H, t, J=8Hz), 7.2-7.5 (10H, m)

FAB MS m/z : 468 (M^+ +1)

(6) Sodium salt of (trans)-[5-(carboxymethoxy)-1-hydroxy-
1,2,3,4-tetrahydro-2-naphthyl)methyl N,N-
diphenylcarbamate

IR (Nujol) : 3400-3200, 1700, 1590 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.2-1.5 (1H, m), 1.6-1.9 (2H, m),
2.2-2.8 (2H, m), 4.06 (2H, s), 4.1-4.4 (3H, m),
6.52 (1H, d, J=7Hz), 6.8-7.1 (2H, m), 7.1-7.5
(10H, m)

FAB MS m/z : 470 (M^+ +1)

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- (7) Sodium salt of (cis)-[5-(carboxymethoxy)-1-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
IR (Nujol) : 3400-3200, 1690, 1590 cm^{-1}
5 NMR (DMSO- d_6 , δ) : 1.4-2.0 (3H, m), 2.2-2.8 (2H, m),
4.10 (2H, s), 4.1-4.4 (3H, m), 6.58 (1H, d, J=8Hz), 6.74 (1H, d, J=8Hz), 7.00 (1H, t, J=8Hz), 7.1-7.5 (10H, m)
FAB MS m/z : 470 (M^++1)
10
- (8) Sodium salt of [5-(carboxymethoxy)-1-fluoro-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
IR (Nujol) : 3400-3300, 1710, 1600 cm^{-1}
15 NMR (DMSO- d_6 , δ) : 1.4-2.2 (2H, m), 2.5-3.2 (2H, m),
3.9-4.5 (4H, m), 5.00 (1H, d, J=52Hz), 6.7-7.5 (13H, m)
FAB MS m/z : 488 (M^++1)
- (9) Sodium salt of [5-(carboxymethoxy)-1,2-methylene-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
IR (Nujol) : 1700, 1600 cm^{-1}
20 NMR (DMSO- d_6 , δ) : 0.8-1.4 (2H, m), 1.7-2.1 (3H, m),
25 3.0 (1H, m), 4.06 (2H, s), 4.10 (1H, d, J=10.8Hz), 4.20 (1H, d, J=10.8Hz), 6.50 (1H, d, J=8Hz), 6.71 (1H, d, J=8Hz), 6.93 (1H, t, J=8Hz), 7.2-7.6 (10H, m)
FAB MS m/z : 466 (M^++1)
30
- (10) Sodium salt of [5-(carboxymethoxy)-2-fluoro-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate
IR (Nujol) : 1700, 1600 cm^{-1}
35 NMR (DMSO- d_6 , δ) : 1.6-2.0 (2H, m), 2.5-3.0 (4H, m),
4.08 (2H, s), 4.25 (2H d, J=20Hz), 6.47 (1H, d,

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J=8Hz), 6.51 (1H, d, J=8Hz), 6.97 (1H, d,
J=8Hz), 7.1-7.5 (10H, m)

FAB MS m/z : 472 (M^+ +1)

- 5 (11) Sodium salt of 2-[5-(carboxymethoxy)-1,2-methylene-
1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate
IR (Nujol) : 1705, 1600 cm^{-1}
NMR (DMSO- d_6 , δ) : 0.5-0.8 (2H, m), 1.0-2.0 (5H, m),
10 2.5-3.0 (2H, m), 4.05 (2H, s), 4.0-4.3 (2H, m),
6.49 (1H, d, J=8Hz), 6.8-7.0 (2H, m), 7.1-7.5
(10H, m)
FAB MS m/z : 480 (M^+ +1)
- 15 (12) Sodium salt of 2-[5-(carboxymethoxy)-2-hydroxy-2-
methyl-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate
IR (Nujol) : 3400, 1700, 1600 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.05 (3H, s), 1.1-2.0 (4H, m),
20 2.0-2.4 (2H, m), 2.75 (1H, m), 4.07 (2H, s),
4.0-4.3 (2H, m), 6.18 (1H, d, J=8Hz), 6.46 (1H,
d, J=8Hz), 6.85 (1H, t, J=8Hz), 7.1-7.5 (10H, m)
FAB MS m/z : 498 (M^+ +1)
- 25 (13) Sodium salt of 2-[5-(carboxymethoxy)-2-methyl-3,4-
dihydro-1-naphthyl]ethyl N,N-diphenylcarbamate
IR (Nujol) : 1700, 1600 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.68 (3H, s), 2.0-3.2 (4H, m),
3.2-4.2 (4H, m), 4.12 (2H, s), 6.5-6.7 (2H, m),
30 7.0-7.8 (11H, m)
FAB MS m/z : 480 (M^+ +1)
- (14) Sodium salt of 2-[5-(carboxymethoxy)-1,2-dihydroxy-
1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
35 diphenylcarbamate

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IR (Nujol) : 3300, 1700, 1590 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.7-2.2 (4H, m), 2.5-2.7 (1H, m),
2.8-3.0 (1H, m), 3.75 (1H, t, $J=5.4\text{Hz}$), 4.0-4.3
(2H, m), 4.38 (2H, s), 6.6-6.8 (1H, m), 7.0-7.4
(12H, m)

FAB MS m/z : 500 (M^++1)

(15) Sodium salt of (cis)-2-[5-(carboxymethoxy)-2-hydroxy-
1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate

IR (Nujol) : 1700, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.5-2.1 (4H, m), 2.4-2.8 (3H, m),
3.83 (1H, m), 4.06 (2H, s), 4.0-4.3 (2H, m),
6.29 (1H, d, $J=8\text{Hz}$), 6.46 (1H, d, $J=8\text{Hz}$), 6.87
(1H, t, $J=8\text{Hz}$), 7.1-7.5 (10H, m)

FAB MS m/z : 484 (M^++1)

(16) Sodium salt of (trans)-2-[5-(carboxymethoxy)-2-
hydroxy-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate

IR (Nujol) : 1700, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.5-1.9 (4H, m), 2.5-2.7 (3H, m),
3.73 (1H, m), 4.06 (2H, s), 4.0-4.3 (2H, m),
6.39 (1H, d, $J=8\text{Hz}$), 6.45 (1H, d, $J=8\text{Hz}$), 6.87
(1H, t, $J=8\text{Hz}$), 7.1-7.5 (10H, m)

FAB MS m/z : 484 (M^++1)

(17) Sodium salt of 2-[5-(carboxymethoxy)-2-fluoro-
1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate

IR (Nujol) : 1700, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.5-2.0 (4H, m), 2.5-2.9 (3H, m),
3.73 (1H, m), 4.08 (2H, s), 4.0-4.3 (2H, m),
6.41 (1H, d, $J=8\text{Hz}$), 6.49 (1H, d, $J=8\text{Hz}$), 6.91
(1H, t, $J=8\text{Hz}$), 7.1-7.5 (10H, m)

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FAB MS m/z : 486 ($M^+ + 1$)

(18) Sodium salt of 2-[5-(carboxymethoxy)-1-hydroxy-
1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-
diphenylcarbamate

IR (Nujol) : 3400, 1700, 1600 cm^{-1} NMR (DMSO-d_6 , δ) : 1.4-2.0 (6H, m), 2.5-2.6 (2H, m),
4.0-4.2 (2H, m), 4.37 (2H, s), 6.58 (1H, t,
J=5Hz), 7.02 (2H, d, J=5Hz), 7.1-7.5 (10H, m)FAB MS m/z : 484 ($M^+ + 1$)

(19) Sodium salt of 2-[5-(carboxymethoxy)-3,4-dihydro-1-
naphthyl]ethyl N,N-diphenylcarbamate

IR (Nujol) : 1700, 1600 cm^{-1} NMR (DMSO-d_6 , δ) : 2.0-2.2 (2H, m), 2.5-2.7 (4H, m),
4.0-4.3 (4H, m), 5.75 (1H, m), 6.63 (1H, d,
J=8Hz), 6.80 (1H, d, J=8Hz), 6.98 (1H, t,
J=8Hz), 7.0-7.4 (10H, m)FAB MS m/z : 466 ($M^+ + 1$)

Example 33

A solution of benzhydryl N-methyl-N-[[1,2,3,4-
tetrahydro-5-(methoxycarbonylmethoxy)-2-
naphthyl]methyl]carbamate (60 mg) in 0.1N sodium hydroxide
(1.27 ml) and methanol was stirred at room temperature
overnight and evaporated in vacuo. The residue was
powdered from n-hexane to afford sodium salt of benzhydryl
N-methyl-N-[[1,2,3,4-tetrahydro-5-(carboxymethoxy)-2-
naphthyl]methyl]carbamate (50 mg) as a pale yellow powder.

mp : 100-105°C

IR (Nujol) : 1695, 1605, 1200 cm^{-1} NMR (DMSO-d_6 , δ) : 1.2 (1H, br m), 1.75-2.05 (2H,
m), 2.25-3.1 (4H, m), 2.87 and 3.08 (3H, s),
3.2-3.4 (2H, m), 4.06 (2H, s), 6.48 (2H, br d),
6.70 (1H, s), 6.94 (1H, br t), 7.2-7.4 (10H, m)

- 106 -

FAB MS : 482 ($M^+ + 1$)Example 34

5 A solution of [1,2,3,4-tetrahydro-5-(methoxycarbonylmethoxy)-2-naphthyl]methyl N,N-diphenylcarbamate (600 mg) in 1N sodium hydroxide aqueous solution (2.0 ml), methanol (7 ml), and 1,2-dimethoxyethane (7 ml) was stirred at room temperature for 40 minutes, neutralized with 1N hydrochloric acid, 10 evaporated in vacuo, and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was washed with n-hexane to afford a colorless powder (500 mg), which was dissolved in a mixture of 15 ethanol (20 ml), methanol (30 ml) and tetrahydrofuran (10 ml). The solution was mixed with 1N sodium hydroxide aqueous solution (1.10 ml) and evaporated in vacuo. The residue was washed with n-hexane to afford sodium salt of [5-(carboxymethoxy)-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (475 mg) as a colorless powder.

IR (Nujol) : 1715, 1625, 1600 (shoulder) cm^{-1} NMR (DMSO-d_6 , δ) : 1.24 (1H, m), 1.83 (2H, m), 2.25-2.81 (4H, m), 4.03-4.08 (4H, m), 6.45-6.52 (2H, m), 6.92 (1H, t, $J=7.8\text{Hz}$), 7.20-7.43 (10H, m)25 FAB MS m/z : 454 ($M^+ + 1$)Elemental Analysis Calcd. for $\text{C}_{26}\text{H}_{24}\text{NNaO}_5$:

C 68.87, H 5.33, N 3.09

Found : C 68.59, H 5.31, N 3.08

30 Example 35

A mixture of 1-[(3,4-dihydro-5-carboxymethoxy)-2-naphthyl]methyl]-5-diphenylmethyl-2(1H)-pyridone (100 mg) and a catalytic amount of 10% palladium on carbon (50% wet) were stirred at room temperature under atmospheric 35 hydrogen gas for 5 hours. The catalyst was filtered off

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and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 5:1) to give 1-[(1,2,3,4-tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-5-diphenylmethyl-2(1H)-pyridone (94.5 mg) as a pale yellow powder.

mp : 162-163°C

IR (Nujol) : 1670, 1610 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.10-1.40 (1H, m), 1.70-4.00 (8H, m), 4.28 (2H, s), 5.39 (1H, s), 6.35-6.55 (4H, m), 6.90-7.00 (1H, m), 7.10-7.50 (11H, m)

MASS (+ APCI) : 480 (M^+ +1)

Example 36

The following compound was obtained according to a similar manner to that of Example 35.

1-[(1,2,3,4-Tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-3-diphenylmethyl-2(1H)-pyridone

mp : 185-187°C

IR (Nujol) : 1730, 1640 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.20-4.00 (9H, m), 4.30 (2H, s), 5.64 (1H, s), 6.15-6.25 (1H, m), 6.45-6.60 (2H, m), 6.70-7.40 (12H, m), 7.55-7.70 (1H, m)

Example 37

Sodium salt of 2-[5-(carboxymethoxy)-2-methyl-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate was prepared from 2-[5-(ethoxycarbonylmethoxy)-2-methyl-3,4-dihydro-1-naphthyl]ethyl N,N-diphenylcarbamate in a similar manner to that of Example 31.

IR (Nujol) : 1700, 1600 cm^{-1}

NMR (DMSO- d_6 , δ) : 0.86 (3H, d, $J=6.4\text{Hz}$), 1.3-2.9 (4H, m), 4.0-4.2 (4H, m), 6.33 (1H, d, $J=8\text{Hz}$), 6.46 (1H, d, $J=8\text{Hz}$), 6.87 (1H, t, $J=8\text{Hz}$), 7.1-

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7.5 (10H, m)

FAB MS m/z : 482 ($M^+ + 1$)Example 38

5 A solution of sodium salt (0.2 g) of (2R)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate in a mixture of water and ethyl acetate was washed with 1N-HCl solution and brine. The dried solvent was removed in vacuo and the
10 residue was recrystallized from ethyl ether to give (2R)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate (150 mg).

 NMR ($CDCl_3$, δ) : 1.6-2.0 (2H, m), 2.6-3.0 (4H, m),
 4.15 (2H, s), 4.64 (2H, s), 6.54 (1H, d, $J=8Hz$),
15 6.69 (1H, d, $J=8Hz$), 7.07 (1H, t, $J=8Hz$),
 7.1-7.5 (10H, m)

20

25

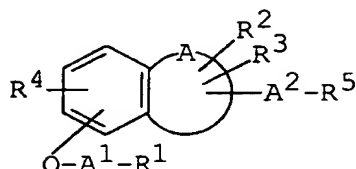
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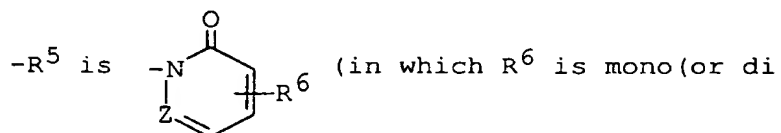
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C L A I M S

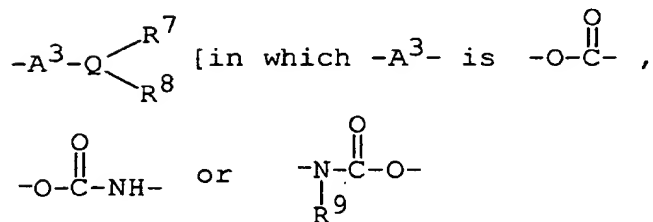
1. A compound of the formula :



10 wherein R¹ is carboxy or protected carboxy,
 R² is hydrogen, hydroxy or protected hydroxy,
 R³ is hydrogen, hydroxy, protected hydroxy,
 lower alkyl or halogen,
 R⁴ is hydrogen or halogen,
 15 A¹ is lower alkylene,
 A² is bond or lower alkylene,



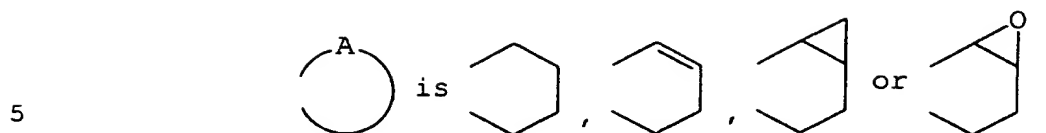
or tri)aryl(lower)alkyl and Z is N or CH), or



(wherein R⁹ is hydrogen or lower alkyl), Q is N or CH, R⁷ is aryl and R⁸

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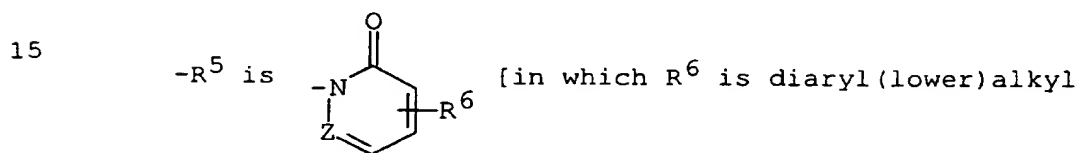
is aryl], and



and a pharmaceutically acceptable salt thereof.

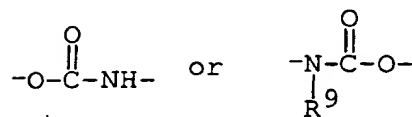
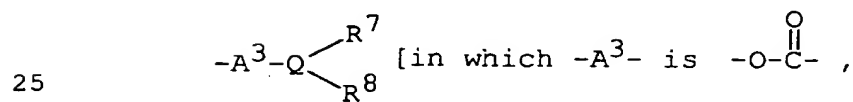
2. A compound of claim 1,

wherein

 R^1 is carboxy or esterified carboxy, A^1 is C_1 - C_3 alkylene, A^2 is bond or C_1 - C_3 alkylene, and

20

and Z is N or CH], or



30

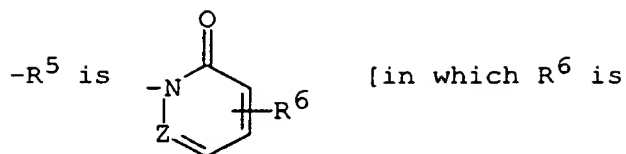
(wherein R^9 is hydrogen or lower alkyl),
 Q is N or CH, R^7 is aryl and R^8 is aryl].

3. A compound of claim 2,

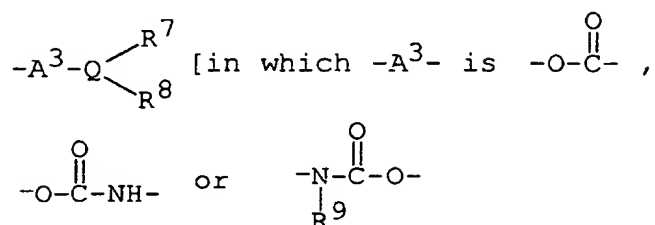
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wherein

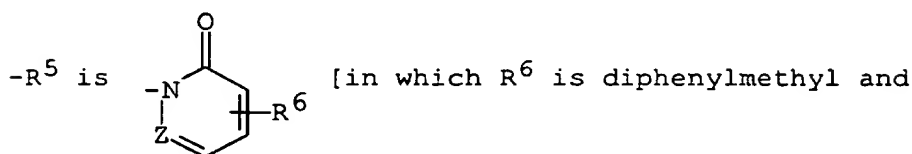


10 diphenyl(lower)alkyl and Z is N or CH], or



20 (wherein R^9 is hydrogen or lower alkyl),
 Q is N or CH, R^7 is phenyl and R^8 is phenyl].

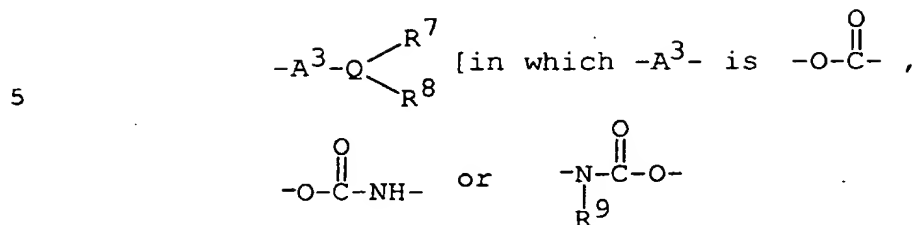
- 25 4. A compound of claim 3, wherein
 R^1 is carboxy or lower alkoxy carbonyl,
 R^2 is hydrogen, hydroxy or acyloxy,
 R^3 is hydrogen, hydroxy, acyloxy, lower alkyl or
 halogen,
 R^4 is hydrogen or halogen,
 A^1 is methylene,
 A^2 is bond, methylene or ethylene, and



35

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Z is N or CH], or

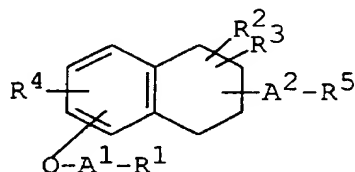


10

(wherein R^9 is hydrogen or lower alkyl),
 Q is N or CH, R^7 is phenyl and R^8 is phenyl].

5. A compound of claim 4, which is a compound of the
 formula :

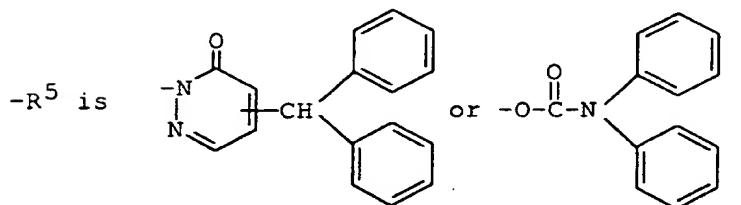
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20

wherein R^1 is carboxy or lower alkoxy carbonyl,
 R^2 is hydrogen or hydroxy,
 R^3 is hydrogen, hydroxy, lower alkyl or
 halogen,
 R^4 is hydrogen or halogen,
 25 A^1 is methylene,
 A^2 is methylene or ethylene, and

30



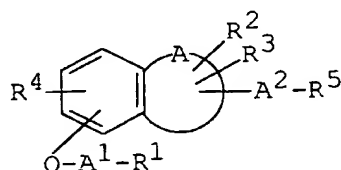
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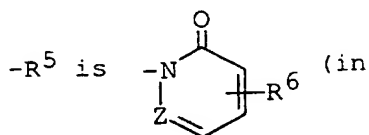
6. A compound of claim 5,
which is selected from the group consisting of

- 5 (1) sodium salt of (2R)-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl N,N-diphenylcarbamate,
- 10 (2) sodium salt of (trans)-2-[5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-1-naphthyl]ethyl N,N-diphenylcarbamate and
- (3) (S)-2-[(1,2,3,4-tetrahydro-5-carboxymethoxy-2-naphthyl)methyl]-6-diphenylmethyl-3(2H)-pyridazinone.

15 7. A process for preparing a compound of the formula :



wherein R^1 is carboxy or protected carboxy,
 R^2 is hydrogen, hydroxy or protected hydroxy,
 R^3 is hydrogen, hydroxy, protected hydroxy,
 25 lower alkyl or halogen,
 R^4 is hydrogen or halogen,
 A^1 is lower alkylene,
 A^2 is bond or lower al

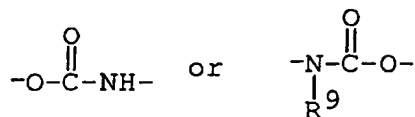
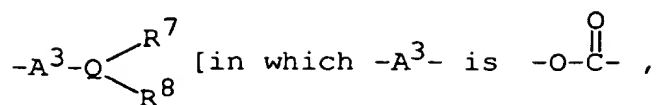


35 or tri)aryl(love

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CH), or

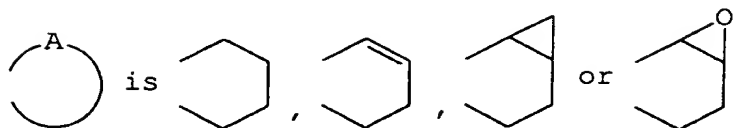
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10

(wherein R^9 is hydrogen or lower alkyl), Q is N or CH, R^7 is aryl and R^8 is aryl], and

15



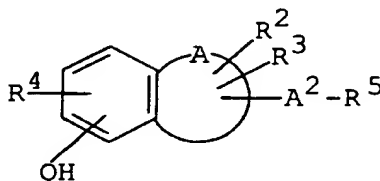
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or a salt thereof,
which comprises

25

(1) reacting a compound of the formula :

30

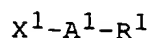


wherein R^2 , R^3 , R^4 , R^5 , A^2 and \bigcirc^A are each as

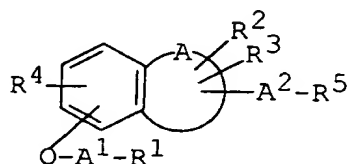
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defined above,
or a salt thereof with a compound of the formula :



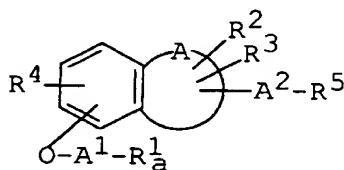
wherein R^1 and A^1 are each as defined above, and
 X^1 is acid residue,
or a salt thereof to give a compound of the formula :



wherein R^1 , R^2 , R^3 , R^4 , R^5 , A^1 , A^2 and \bigcirc^A are

each as defined above,
or a salt thereof, or

(2) subjecting a compound of the formula :



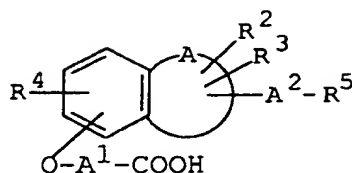
wherein R^2 , R^3 , R^4 , R^5 , A^1 , A^2 and \bigcirc^A are each

as defined above, and
 R_a^1 is protected carboxy,
or a salt thereof to elimination reaction of the

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carboxy protective group to give a compound of the formula :

5



10

wherein R^2 , R^3 , R^4 , R^5 , A^1 , A^2 and \textcircled{A} are each as

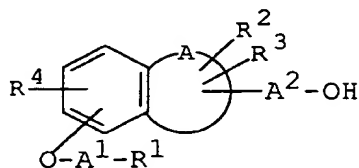
defined above,

or a salt thereof, or

15

(3) reacting a compound of the formula :

20



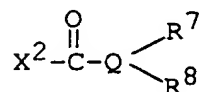
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wherein R^1 , R^2 , R^3 , R^4 , A^1 , A^2 and \textcircled{A} are each

as defined above,

or a salt thereof with a compound of the formula :

30



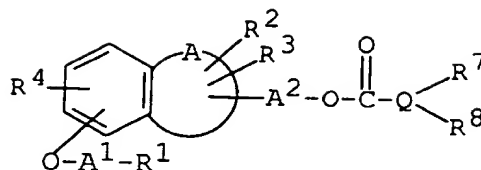
wherein R^7 , R^8 and Q are each as defined above, and X^2 is halogen,

35

or a salt thereof to give a compound of the formula :

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5



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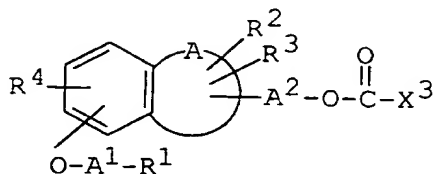
wherein R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , A^1 , A^2 , Q and \textcircled{A}

are each as defined above,
or a salt thereof, or

15

(4) reacting a compound of the formula :

20



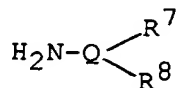
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wherein R^1 , R^2 , R^3 , R^4 , A^1 , A^2 and \textcircled{A} are each as

30

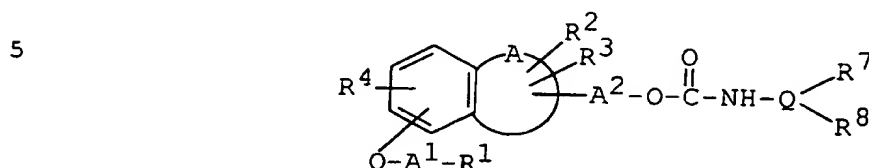
defined above, and
 X^3 is halogen,
or a salt thereof with a compound of the formula :

35



- 118 -

wherein R^7 , R^8 and Q are each as defined above,
or a salt thereof to give a compound of the formula :

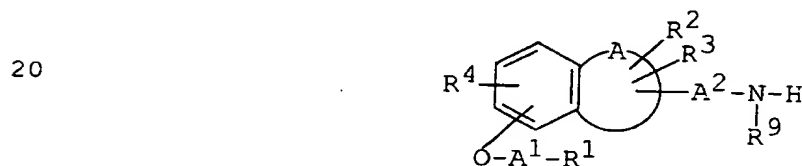


10

wherein R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , A^1 , A^2 , Q and \textcircled{A}

are each as defined above,
or a salt thereof, or

15 (5) reacting a compound of the formula :

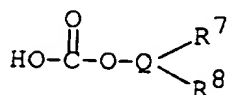


25

wherein R^1 , R^2 , R^3 , R^4 , R^9 , A^1 , A^2 and \textcircled{A} are each

as defined above,
or a salt thereof with a compound of the formula :

30

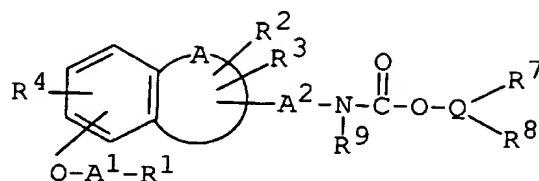


wherein R^7 , R^8 and Q are each as defined above,
or its reactive derivative at the carboxy group
or a salt thereof to give a compound of the formula :

35

- 119 -

5



10

wherein R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , A^1 , A^2 , Q and



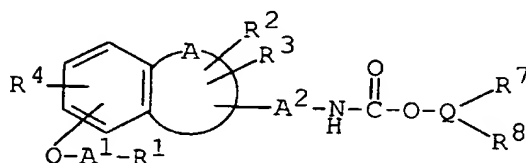
are each as defined above,

or a salt thereof, or

15

(6) reacting a compound of the formula :

20



25

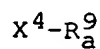
wherein R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , A^1 , A^2 , Q and



are each as defined above,

30

or a salt thereof with a compound of the formula :



wherein R_a^9 is lower alkyl and

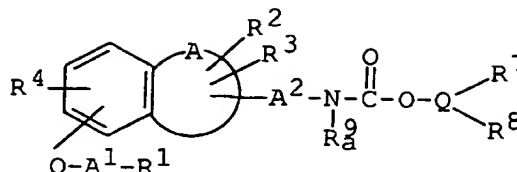
35

X^4 is halogen,

or a salt thereof to give a compound of the formula :

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5



10

wherein R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R_a^9 , A^1 , A^2 , Q and



are each as defined above,

15

or a salt thereof.

20

8. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

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9. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a prostaglandin I_2 agonist.

30

10. A method for treating or preventing arterial obstruction, restenosis after percutaneous transluminal coronary angioplasty, arteriosclerosis, cerebrovascular disease or ischemic heart disease which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

35

11. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 95/00373

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/64 C07D237/14 C07C271/28 C07C235/40 A61K31/44
A61K31/50 A61K31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 542 203 (ONO PHARMACEUTICAL CO., LTD.) 19 May 1993 cited in the application see the whole document -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

26 April 1995

Date of mailing of the international search report

- 9. 05. 95

Name and mailing address of the ISA

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Authorized officer

Bosma, P

Information on patent family members

PCT/JP 95/00373

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/00373

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.